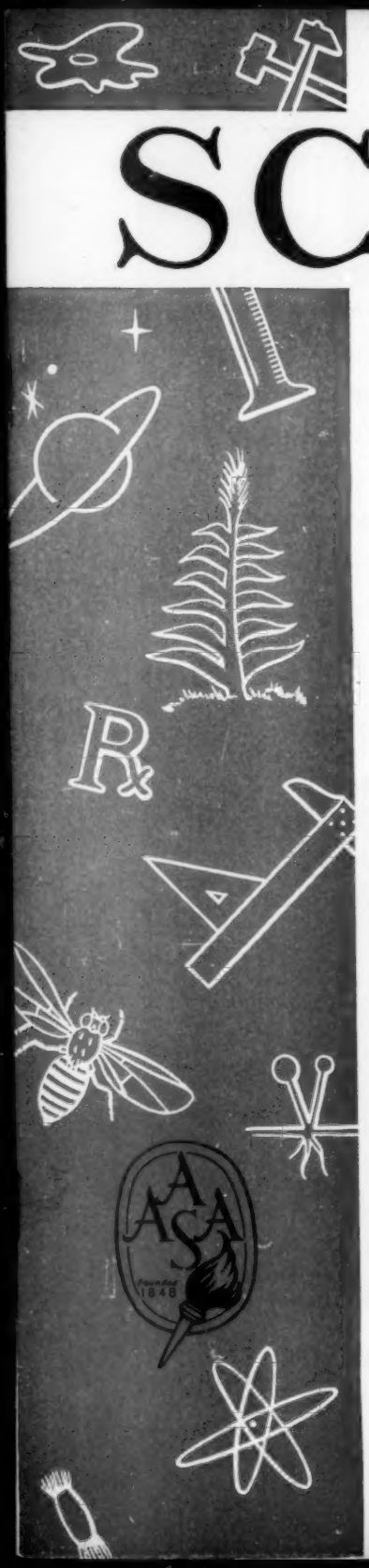

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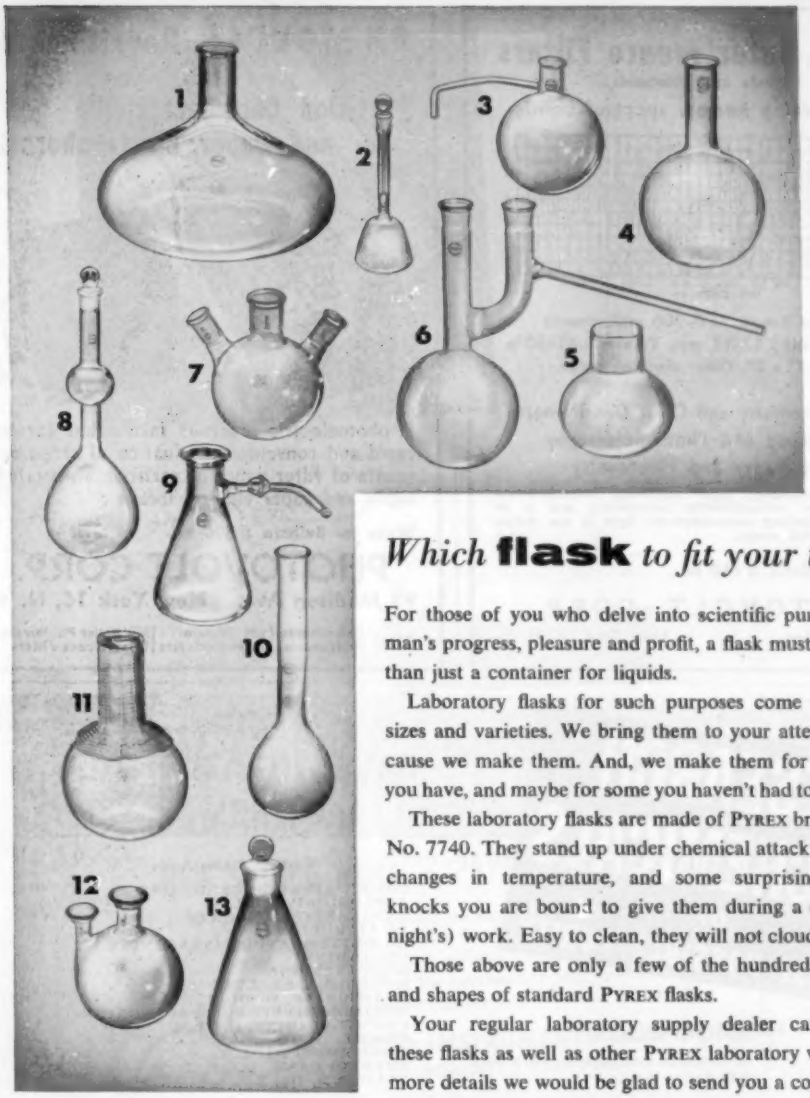

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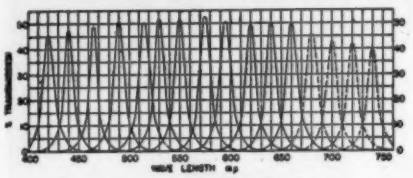

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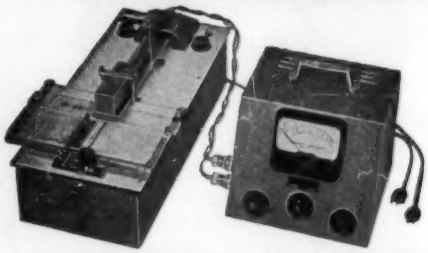

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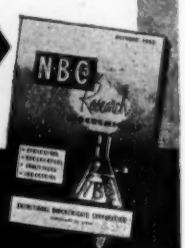

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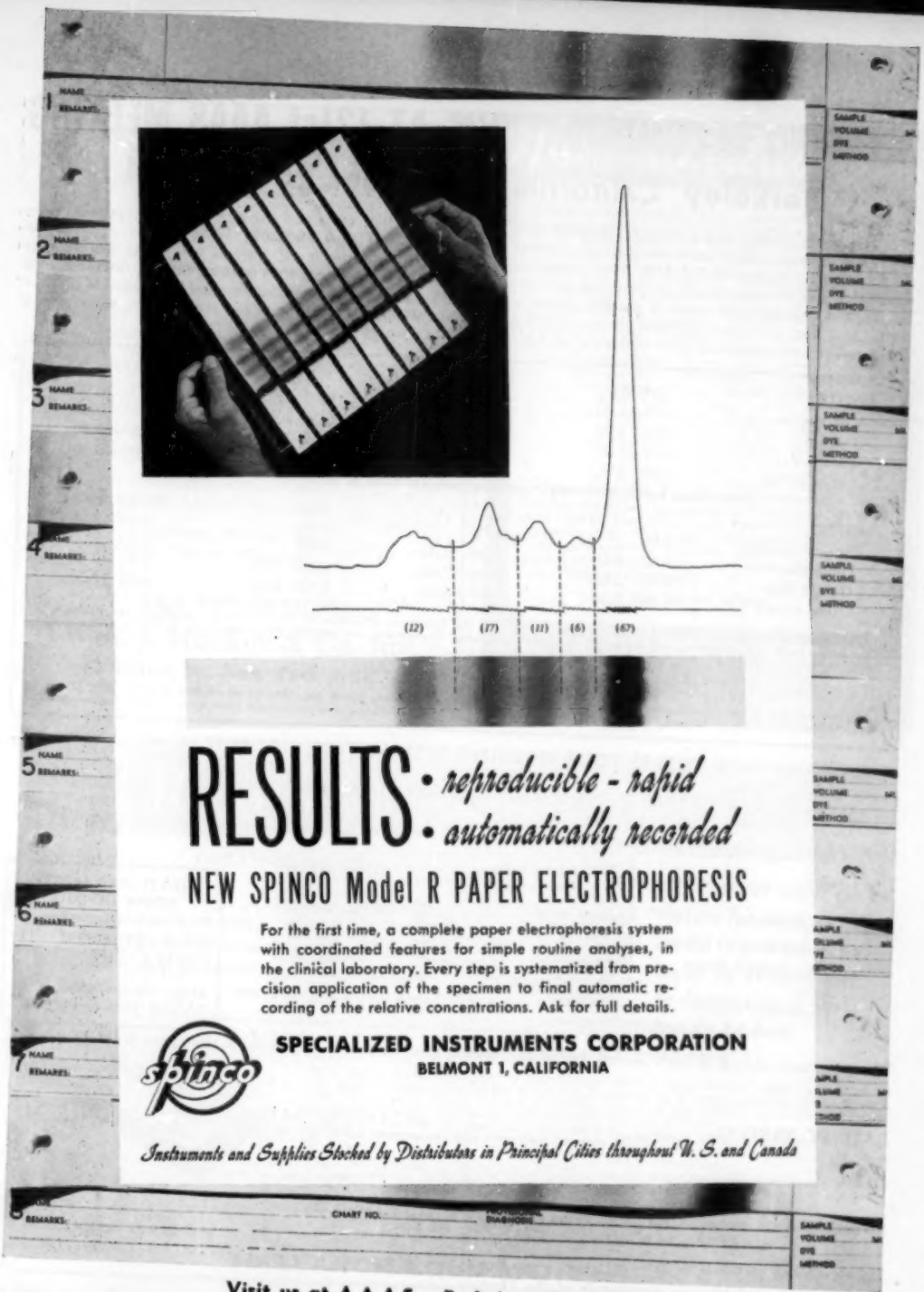

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Berkeley, California, December 26-31, 1954

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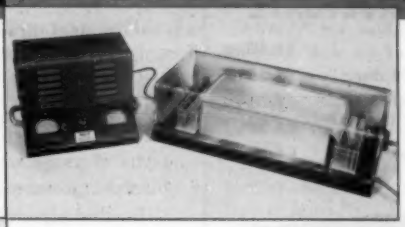

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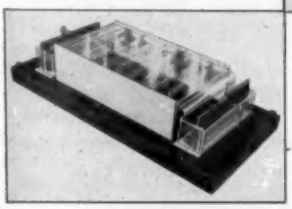

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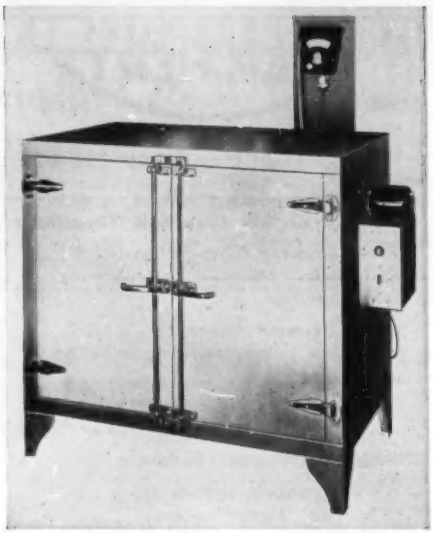

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That Which Is the Spirit of Christmas

That some authors have been bothered—in a couple of instances incensed—by our proclivity for "which hunting" is shown by their reactions to the edited manuscripts returned to them for approval at the time of acceptance. Perhaps their hearts may be softened a little, especially in view of the imminent Christmas season, by this short and delightful piece that appeared in "The Talk of the Town" of The New Yorker *for 25 December 1948, page 11. Copyrighted 1948 by The New Yorker Magazine, Inc., it is reprinted here by permission.—D. R.; C. V. M.*

WE had a Scrooge in our office a few minutes ago, a tall, parched man, beefing about Christmas and threatening to disembowel anyone who mentioned the word. He said his work had suffered and his life been made unbearable by the demands and conventions of the season. He said he hated wise men, whether from the East or from the West, hated red ribbon, angels, Scotch Tape, greeting cards depicting the Adoration, mincemeat, dripping candles, distant and near relatives, fir balsam, silent nights, boy sopranos, shopping lists with check marks against some of the items, and the whole yuletide stratagem, not to mention the low-lying cloud of unwritten thank-you letters hanging just above the horizon. He was in a savage state. Before he left the office, though, we saw him transfigured, just as Scrooge was transfigured. The difference was that whereas Scrooge was softened by visions, our visitor was softened by the sight of a small book standing on our desk—a copy of Fowler's *Modern English Usage*.

"Greatest collection of essays and opinions ever assembled between covers," he shouted, "including a truly masterful study of *that* and *which*."

He seized the book and began thumbing through it for favorite passages, slowly stuffing a couple of small gift-wrapped parcels into the pocket of his greatcoat.

"Listen to this," he said in a triumphant voice: "'Avoidance of the obvious is very well, provided that it is not itself obvious; but, if it is, all is spoilt.' Isn't that beautiful?"

We agreed that it was a sound and valuable sentiment, perfectly expressed. He then began a sermon on *that* and *which*, taking as his text certain paragraphs from Fowler, and warming rapidly to his theme.

"Listen to this: 'If writers would agree to regard *that* as the defining relative pronoun, and *which* as the nondefining, there would be much gain both in lucidity and in ease. Some there are who follow this principle now; but it would be idle to pretend that it is the practice either of most or of the best writers.'"

"It was the practice of St. Matthew," we put in hastily. "Or at any rate he practiced it in one of the most moving sentences ever constructed: 'And, lo, the star, which they saw in the east, went before them, till it came and stood over where the young child was.' You've got to admit that the *which* in that sentence is where it ought to be, as well as every other word. Did you ever read a more satisfactory sentence than that in your life?"

"It's good," said our friend, cheerfully. "It's good because there isn't a ten-dollar word in the whole thing. And Fowler has it pegged, too. Wait a minute. Here. 'What is to be deprecated is the notion that one can improve one's style by using stylish words.' See what I mean about Fowler? But let's get back to *that* and *which*. That's the business that really fascinates me. Fowler devotes eight pages to it. I got so excited once I had the pages photostatted. Listen to this: 'We find in fact that the antecedent of *that* is often personal.' Now, that's very instructive."

"Very," we said. "And if you want an example, take Matthew 2: 1: '. . . there came wise men from the east to Jerusalem, saying, Where is he that is born King of the Jews?' Imagine how that simple clause could get loused up if someone wanted to change *that* to *who*!"

"Exactly," he said: "That's what I mean about Fowler. What was the sentence again about the star? Say it again."

We repeated, "And, lo, the star, which they saw in the east, went before them, till it came and stood over where the young child was."

"You see?" he said, happily. "This is the greatest damn book ever written." And he left our office transfigured, a man in excellent spirits. Seeing him go off merry as a grig, we realized that Christmas is where the heart is. For some it is in a roll of ribbon, for some in the eyes of a young child. For our visitor, we see clearly, Christmas was in a relative pronoun. Wherever it is, it is quite a day.

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Auxiliary Infectious Nucleoprotein from Plants Infected with Tobacco Mosaic Virus

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PLANTS infected with tobacco mosaic virus (TMV) synthesize massive quantities of infectious material. When this material is extracted from long-infected plants and compared with the inoculum, it appears to be a replica of the latter with respect to biological, chemical, and physical properties. Such an observation implies a rigid relationship between the chemical composition of TMV and its biological specificity. It suggests that virus reduplication is achieved by replication of the specific nucleoprotein introduced into the cell by inoculation.

The experimental evidence for the apparent identity between the TMV inoculum and the final product of the reduplication process depends on analyses of the nucleoprotein extracted by common neutral buffers from infected leaf, for TMV is readily soluble in such buffers. Our attention was directed to the leaf proteins *not* found in such extracts by the observation that TMV-infected leaf synthesizes an excess (as compared with otherwise identical healthy tissue) of buffer-insoluble nucleoprotein. The excess reaches a maximum in advance of the appearance of TMV and declines in amount as the virus accumulates in the tissue (*1*).

This evidence of a close relationship between insoluble nucleoprotein and TMV has led us to compare the insoluble nucleoprotein components of infected and uninfected leaf. The present paper summarizes the initial results of this investigation (*2*). It describes the isolation and partial characterization of a hitherto unknown buffer-insoluble nucleoprotein which is consistently associated with TMV infection. This protein is infectious, and appears to possess biological properties indistinguishable from those of the virus. However, the new nucleoprotein, although similar to TMV in composition, differs significantly from ordinary virus with respect to amino acid composition and certain physical properties.

When tobacco leaf is homogenized in *p*H 7.0 phosphate buffer (0.05*M*) and the homogenate is centrifuged at about 2500 *g*, the soluble proteins of the supernate, which include TMV, represent about one-half of the total protein content of the leaf. If the thoroughly washed residue is then extracted in 10-percent NaCl for 18 hr at 4°C, about 15 percent of the previously insoluble protein and almost all of the nucleic acid become solubilized. A number of components can be isolated from this extract by suitable procedures, such as dilution, salting-out, and ultracentrifugation. When such extracts of comparable infected and uninfected tobacco leaf are prepared and the high-molecular weight components are isolated by ultracentrifugation (1 hr at 104,500 *g*) a prominent component not found in extracts of normal tissue is observed in infected material. Results of such parallel fractionation are shown in Fig. 1. The ultracentrifuge pellet containing the high molecular weight material from uninfected tissue, which is readily redissolved in *p*H 7.0 phosphate buffer, on electrophoretic analysis shows the presence of a fast-moving component (mobility at *p*H 7.0 = -18×10^{-5} cm²/v/sec) and poorly resolved slow-moving components with mobilities at *p*H 7.0 ranging from −4 to −7. These components are present in comparable extracts prepared from infected tissue, but the infected material also contains an additional component of mobility = −8.5, which has been given the designation I8.

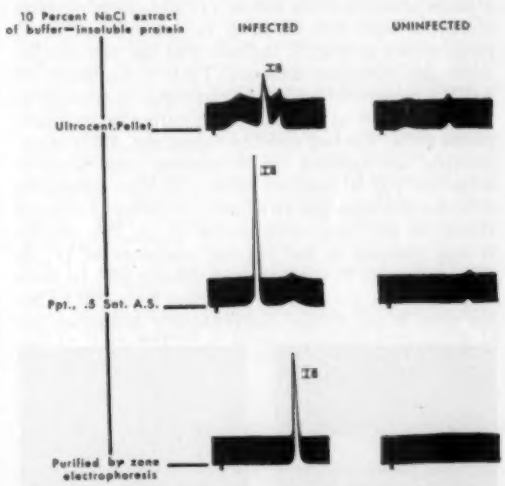

Fig. 1. Descending electrophoresis patterns of comparable infected and uninfected material. Migration is to the right from the marked starting boundaries. Times and currents for all but the lower left-hand pattern were 51 to 60 min and 7.7 to 7.8 ma. In the latter pattern, migration time was 83 min at a current of 7.8 ma. The crude 10-percent NaCl extract is ultracentrifuged and the resulting pellet dissolved in *p*H 7.0 phosphate buffer. The precipitate obtained from this solution by salting out with 0.5 saturated ammonium sulfate is finally purified by zone electrophoresis.

Component I8 can be isolated from the crude high molecular weight fraction in an electrophoretically homogeneous form by salting out in 0.5 saturated ammonium sulfate (which precipitates I8, but fails to precipitate the normal slow components), followed by zone electrophoresis on a starch column (*3*), which separates I8 from the fast-moving normal component. When this procedure (outlined in Fig. 1) is applied to the extracts of infected tissue, electrophoretically homogeneous preparations of I8 are obtained. Systemically infected tobacco leaf yields 10 to 50 μg of I8 per gram wet weight. The average yield of TMV is about 2500 μg/g. The new protein has been found consistently in a series of eight preparations from infected leaf and has never been detected in uninfected tissue. We conclude therefore that I8 is a specific component uniquely present in the insoluble residue of TMV-infected leaf.

Several different preparations of I8 have been purified as described in the preceding paragraph and partially characterized with the following results.

1) *Size and shape.* Electron micrographs of I8 and of the TMV isolated from the same tissue are shown in Fig. 2. Both are rods averaging about 450 mμ in length. The frequency distribution of the lengths of I8 and TMV rods obtained from such photographs show no significant differences between the two components.

2) *Electrophoretic mobility.* Preparations of I8 and of TMV from the same tissue were dialyzed against a series of common-ion buffers (*4*) and electrophoretic mobilities were determined at various *p*H's. The results, shown in Fig. 3, indicate that the two components are distinctly different. TMV is isoelectric at *p*H 3.4, precipitating as characteristic microneedles. I8 is isoelectric at *p*H 2.9, precipitating in an amorphous form. The two mobility curves also differ qualitatively; the mobility of I8 becomes more negative when the *p*H is dropped below 7.0. This anomalous behavior indicates that the lower *p*H induces a marked change in the ionic configuration of I8. This change is also reflected in the physical character of I8; at *p*H's below 5.0, I8 tends to form viscous gels. In these respects I8 is qualitatively different from TMV, for the virus shows neither electrophoretic anomalies nor

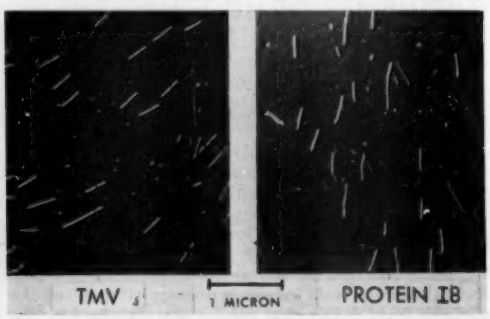

Fig. 2. Electron micrographs (Palladium-platinum shadowed) of concurrently isolated preparations of I8 and TMV.

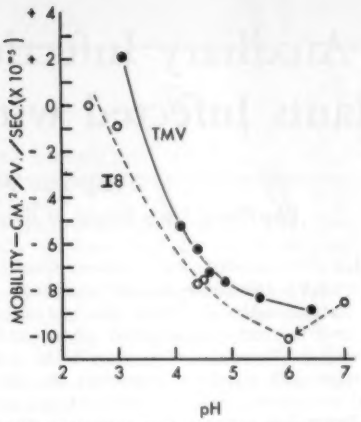

Fig. 3. Electrophoretic mobility of concurrently isolated preparations of I8 and TMV at various *p*H's. All samples were dissolved in buffers of ionic strength 0.1, which contained NaCl to provide common ions (*4*).

gel formation at low *p*H's. When a mixture of equal amounts of TMV and I8 is brought to *p*H 5, the resulting gel contains the TMV as well as I8. This suggests that I8 and TMV tend to combine under these conditions. One result of this phenomenon is that mixtures of the two proteins cannot be resolved electrophoretically.

3) *Chemical composition.* Several samples of electrophoretically homogeneous preparations of I8 and concurrently isolated TMV have been hydrolyzed and analyzed for amino acid composition by the method of Fischer and Dörfel (*5*). Table 1 shows the results obtained from quadruplicate analyses of identical amounts of I8 and TMV based on chromatogram sheets carrying hydrolyzates of both proteins and six samples of a standard calibration mixture of amino acids. The analyses reveal an over-all general similarity between I8 and TMV. However, the proteins are not identical. Most apparent is the relatively large difference in the tyrosine contents of the two proteins. This difference has been confirmed by three additional parallel partial analyses of I8 and TMV for this amino acid. The results, which are presented in Table 2, show a consistently lower tyrosine content in I8 than in TMV, the average difference being about 50 percent of the larger value. Table 1 suggests that the amino acid composition of I8 and TMV may also differ with respect to other components, notably serine and glycine, but these possible differences need to be confirmed. Nevertheless, at least on the basis of the tyrosine values, we conclude that the protein moieties of I8 and TMV are not identical in amino acid composition.

Samples of I8 and concurrently isolated TMV were analyzed for nucleic acid content by extraction with hot 0.5*M* perchloric acid. The average nucleic acid contents of I8 and TMV calculated from Kjeldahl analysis of the samples and the optical densities of perchloric acid extracts at 260 mμ were 5.2 and 5.1

Table 1. Percentage composition of I8 and TMV. Amino acid analysis is based on acid hydrolyzate and therefore does not include tryptophane which represents 2.1 percent of ordinary TMV protein.

Amino acid	I8	TMV	Average deviation of mean
Alanine	5.6	5.6	0.2
Aspartic acid	9.9	11.3	.6
Arginine	13.4	14.4	*
Cystine	0.6	0.5	.1
Glutamic acid	12.4	11.4	.3
Glycine	2.0	1.5	.1
Lysine	2.7	2.5	.5
Phenylalanine	7.5	8.7	1.2
Serine	6.6	7.6	0.2
Threonine	9.0	9.1	.5
Tyrosine	1.8	3.3	.5
Valine	6.8	7.2	.8
Leucine, isoleucine, and proline	17.0	14.2	1.4
Total protein	95.3	97.3	
Nucleic acid	5.2	5.1	
Total nucleoprotein	100.5	102.4	

* Only one value obtained.

Table 2. Percentage tyrosine content of I8 and TMV.

Preparation	I8	TMV	Average deviation of mean
1	2.1	3.4	0.2
2	2.1	2.8	.03
3	1.8	3.5	.1
4*	1.8	3.3	.5
Avg.	2.0	3.5	

* These values obtained from the analysis shown in Table 1.

percent, respectively. There appears to be no significant gross difference in nucleic acid content. Limited amounts of I8 nucleic acid were available for analysis with respect to nitrogen base content. Hydrolysis in 70-percent perchloric acid for 1 hr, followed by paper chromatography (*6*) yielded four ultraviolet-absorbing spots that were identified as adenine, guanine, cytosine, and uracil. Quantitative analysis of these chromatograms, although insufficient to give final results, suggests that the molar ratios of the four bases in I8 may be different from the ratios given by the nucleic acid of concurrently isolated TMV.

These results show that I8 is a pentosenucleoprotein that differs from TMV with respect to amino acid composition and, possibly also, with respect to nitrogen base ratios.

4) *Immunochemical properties.* Figure 4 compares the precipitin curves obtained when various amounts of I8 and concurrently isolated TMV are reacted with 0.001 ml of anti-TMV rabbit serum according to the method of Heidelberger and Kendall (*7*). The two

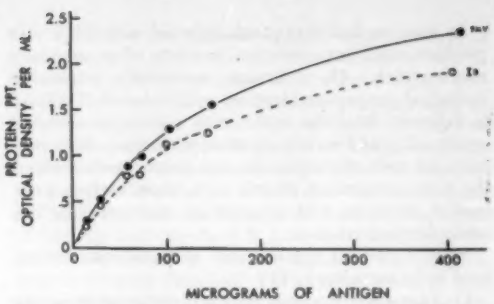

Fig. 4. Precipitin curves yielded by various amounts of concurrently isolated preparations of I8 and TMV. In each case the antigen was reacted with 0.001 ml of anti-TMV rabbit serum. Protein contents of precipitates determined by the Folin phenol method and reported as optical density at 750 mμ.

curves are essentially identical. This observation is evidence of a close immunochemical relationship between I8 and TMV.

5) *Biological properties.* The infectivity of I8 and concurrently isolated TMV have been compared by local-lesion tests on leaves of *Nicotiana glutinosa*. A series of comparable concentrations of the two nucleoproteins were rubbed on opposite halves of *N. glutinosa* leaves. Lesions were examined and counted after 3 days. Both I8 and TMV produced lesions that were indistinguishable in appearance and emerged on the leaf at the same time after inoculation. Lesion counts given by various concentrations of I8 and TMV (Table 3) show that there is no significant difference in the specific infectivity of the two nucleoproteins.

When I8 is rubbed on leaves of *N. tabacum*, symptoms typical of TMV-infected plants become evident in the newly formed leaves. Analysis of leaves infected in this way shows that they contain ordinary buffer-soluble TMV. Parallel groups of plants inoculated with I8 and TMV were found after 13 days to contain 1.1 and 1.3 mg/g of ordinary soluble TMV, respectively. Thus, plants inoculated with I8 produce TMV and show the typical symptoms of infection with TMV. With respect to these biological properties, I8 and TMV do not appear to differ.

Table 3. Comparative infectivity of I8 and TMV.

Preparation	No. of lesions per 4 half-leaves of *N. glutinosa**					
	0.020 mg/ml		0.050 mg/ml		0.100 mg/ml	
	I8	TMV	I8	TMV	I8	TMV
1	20	18	32	39	130	63
2	16	12	40	51	54	25
3	28	22	29	56	25	104

* In each case, parallel numbers represent lesions given by comparable concentrations of I8 and TMV inoculated on opposite halves of the same four leaves.

In sum, we find that plants infected with TMV also produce small but consistent amounts of an auxiliary nucleoprotein, I8. Although apparently possessing biological properties identical with those of TMV, I8 is different from the latter with respect to chemical composition and certain physical properties. Both proteins are rods of similar size and shape, contain about the same amount of nucleic acid, show certain similarities in amino acid composition, and are close immunochemical relatives.

Several possible explanations of these observations need to be considered (*8*):

1) *That I8 is a strain of TMV different from the common form used as inoculum.* This proposal would imply either that I8 was present as a contaminant in the original inoculum, or that it originated by mutation in the infected leaf. However, the biological properties of TMV and I8 appear to be identical. Furthermore, no TMV-related virus strain is known that is not initially soluble in buffer. It is unlikely, therefore, that I8 represents a virus strain different from the common TMV used as inoculum.

2) *That I8 represents an intermediate or alternative product of the specific biosynthesis of ordinary TMV.* This proposal coincides most closely with the information on hand at present. The two proteins are equally characteristic products of plants infected with TMV. They appear to be biologically identical and are very similar in composition. These facts indicate that I8 and TMV are common products of the specific biosynthetic processes induced in the host by the entering TMV inoculum.

The distinct differences that we find in the composition and physical properties of I8 and TMV lead to the further conclusion that the biological specificity of the virus is not rigidly dependent on the particular chemical structure ascribed to ordinary TMV. This conclusion is subject to two alternative interpretations: (i) In the reduplication of the virus, a certain range of latitude in the chemical composition of the product is tolerated without discernible alterations in biological specificity. In this view, I8 would represent one of the allowed alternative structures of the virus, its distinguishing physical properties and cellular location being a consequence of slight, biologically inconsequential chemical differences from ordinary TMV. (ii) Alternatively, the foregoing results may be construed as evidence that the biological specificity of the virus is determined by only part of the chemical structure of ordinary TMV, and that this determinative subunit is present in both I8 and TMV.

Within either interpretation, consideration must also be given to the possibility that I8 is the initial form in which the virus is synthesized, being subsequently converted to the soluble TMV commonly found in the infected plant. Further investigations of these relationships should help to illuminate the biochemistry of TMV reduplication.

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The "Atomic" Rivals

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DEVELOPMENTS in the domain of atomic energy are going to affect our future profoundly. Already it is clear that all our ideas about defense and the role of conventional weapons will soon have to undergo a radical change. (Even though the general public does not yet seem to have realized all the implications of the latest development, the "cheap" hydrogen bomb.)

The development of atomic power for industry is a comparatively long-term project, but its consequences will be almost as far-reaching as in the weapons field. Probably the first really important changes will be seen in those underdeveloped countries where a relatively small-scale provision of power would make a great difference. Nuclear fuels will not have such a marked impact on the more highly industrialized countries which now depend on coal and oil for their power, if only because of the much longer time needed to change over their enormous power systems to nuclear energy. As I have discussed elsewhere [in

* Reprinted by permission from the *Financial Times* (London), 6 Aug. 1954, with the thought that our readers may be interested in seeing how the position looks from the other side of the Atlantic. Sir Francis is professor of thermodynamics at Oxford.

a contribution to *Atomic Energy, A Survey* (Taylor and Francis, London, 1954)], a really large-scale takeover from the conventional fuels can hardly occur before the end of this century, and it will probably be the middle of next century before we can rely mainly on nuclear fuels. However, such an extended timescale should not blind us to the fact that this country has to make a big effort very soon in order to avoid being left in the cold by the eventual exhaustion of our ordinary fuels. Moreover, the export of nuclear power stations to the underdeveloped countries offers Britain possibilities of the greatest economic importance.

Under these circumstances, it is natural to ask what countries have most chance of success in the field of nuclear energy. First of all, since the expenditure connected with atomic development has to be counted in thousands of millions of pounds, only countries that have a very high technologic and scientific potential can compete. This at present limits the field to the United States and the U.S.S.R., on a smaller scale Britain, and later on perhaps Germany. Smaller countries can hardly hope to compete successfully, at least at the moment, even though the quality of their scientists and engineers may be just as high (if not sometimes higher) than in the countries just mentioned. Of course, if fissile material were made available to these smaller countries as is envisaged by the Eisenhower Plan, they also may come into the picture. For today's discussion, however, it is sufficient to regard the United States, the Soviet Union, and Great Britain as the countries chiefly concerned.

Success will depend mainly on the way in which the natural assets of each country are utilized, and the most important of these assets is the country's scientific and technologic manpower. Let us first compare the West with the Russians. The Russians have always had some excellent scientists, but in the past the West has had many more of them. Although this inferiority in numbers is no longer so marked, many people, including myself, had hoped that Russia, as a result of enforcing an ideological strait jacket on her scientists, would never become a serious competitor. This hope seems to have been a false one. As far as one can judge, Russian scientists—at least in most subjects of direct practical importance—seem able to get away with lip service to the Communist ideology and can do more or less as they want to. Certainly a lot of excellent work is now being published by Russian scientists.

But are they not very far behind in their technology? It is difficult to see why this popular belief can still remain so widespread after everything we know about the quantity and quality of their artillery, ammunition, tanks, and aircraft during the war—all produced under most difficult conditions. The real position with respect to scientific and technologic manpower does not seem to be realized in the West. The output of science and technology graduates in the U.S.A. has been falling more or less continually from 1950 onward, while in the U.S.S.R. it is going up all the time; the indications are that the Soviet's annual output is now twice that of the U.S.A.! In addition, we can be sure that the Russians are concentrating a higher percentage of their effort on essential projects, such as atomic energy, than can be done in the West where no government dare starve its people of consumer goods.

Thus, there is a *very real danger* that the Russians are going to overtake us in the atomic field by putting a bigger effort into it. Perhaps the most serious aspect of the spy hunt in the U.S.A. is that it misleads the public into believing that the Russians can progress only by stealing "secrets." The supreme error in war, hot or cold, is to underestimate one's adversary. Indeed it is difficult to imagine anybody doing more to help the Russians than those people who, for whatever purpose, create an atmosphere of spy hysteria.

This question of espionage is now so much in the public mind that we must discuss it in some more detail. In view of the enormous power of the atomic bomb, it is obvious that at first all atomic energy work had to be fenced in by security regulations, just as any important military operation is. For instance, the very fact that work was being done on nuclear fission was an important secret in the war against Germany. Now, not only has the adversary changed, but the whole position as well.

The physics of the release of nuclear energy for either war or peaceful purposes is now almost universal knowledge. The really important information is the technical know-how. In most modern industrial processes this know-how is a complex sum of technical and scientific knowledge and art which cannot be described even in the most lengthy patent description. (Indeed the last decades have seen a decline in the importance of the patent for just this reason.) In order to sell the know-how of a technical process from one firm to another, it is now quite common for teams of highly skilled people to be sent off for years to the purchaser in order to give him the benefit of the new development. To suggest that such knowledge could be acquired and handed over to an enemy by one or two persons, whispering a few words over the lunch table or by stealing some "secret formula," is simply not realistic.

Now let us assume for the sake of argument that some important information is handed over to a potential enemy. How much benefit could be obtain from it? One could tell almost anything to technically underdeveloped countries and it would not help them one iota, simply because they have not the necessary scientific and technologic resources to make use of it. Only a country that is at practically the same technologic level as that from which the information originates could derive any material benefit. However, such a country is just as likely to make new developments under its own steam as to have to rely on outside sources. Whether we like it or not, we have to realize that, although the Russians started somewhat later than the West and although they very probably still have fewer weapons than we do, they are now equal to us in their knowledge of the techniques of "atomic"

war and peace. The "secret" of the latest hydrogen bomb, the "cheap" one, was certainly not stolen from the United States—it was actually developed earlier by the Russians!

What is responsible for the remarkable preoccupation of the U.S.A. with spying? Part of the explanation may be the curious ideas held by the general public about the nature of scientific progress and about the way scientists work. Indeed many people say, "Well, the danger is perhaps overrated, but what does it matter, one can never be *too* safe." They ignore the most important point. Scientific and technologic progress does not come about as the films would have us believe: a man sits in his study or fiddles at some weird looking instrument and suddenly the great inspiration comes, and that is all. Ideas are, of course, an essential part of every new advance, but ideas develop much better in an atmosphere of close contact with one's colleagues. Criticism, friendly or even unfriendly, plays an essential role. Without an exchange of ideas and the ensuing cross-fertilization, developments are intolerably retarded. To try to achieve 100-percent "security" by locking every person up in his little cell, would result in 90-percent sterility. One must therefore strike a balance between making the exchange of information and ideas as free as possible (in order to accelerate the development) and preventing certain important *and* easily transmittable information (which of course still exists, as for example, the size of the effort) from reaching the enemy.

It is very probable that the Russians were helped in the beginning by information obtained from spies, and nobody advocates carelessness over atomic matters. (In particular, sabotage may play a very important role in or just before a future war.) We have, however, to realize that Russia's main strength in the nuclear field is now her own excellence in science and technology and the magnitude of her effort. Security regulations are necessary, but they should be handled with a minimum of interference with the normal practice of science and technology; otherwise we do enormous harm to our own effort.

How far the Americans have deviated from a sane compromise is evident if we have a look at what is happening at the present moment in their country. Here I only want to mention one case that is of particular interest to us. Some months ago a visa was refused to the theoretical physicist, Dirac, one of the most famous and highly respected members of the scientific community, not only of Britain, but of the world. This refusal was made under the terms of the section of the Immigration and Naturalization Act which, to quote the American journal *Physics Today*, "covers categories of undesirables ranging from vagrants to stowaways." In a letter of protest to the press, some leading American physicists said:

> If this is what the McCarran Act means in practice, it seems to us a form of organized cultural suicide. We are very strongly aware of the advantages to this country of Professor Dirac's proposed visit. We are aware of no disadvantage. We also know that his case is only a particularly obvious example of a general policy which operates to this country's detriment.

The picture is a very depressing one. We see the West faced with a rising flood of Communist expansion. However, instead of doing everything to insure technologic superiority, the Americans are busy at places where the danger is largely imaginary, and in doing so immobilize and antagonize the scientists, the very people who are essential for our defense.

I now want to say a few words about the *peaceful aspects of atomic power*. It is true that these problems have not the same degree of urgency as the military applications, but—if we survive the next decades—they will eventually be of paramount importance. Here again progress will be determined largely by the availability of scientists and technologists and by how we make use of them.

At the moment all three countries seem to have reached about the same stage. A medium-size nuclear power station is reported to have started operation in Russia, while quite sizable stations can be expected to operate in Britain and the States within 2 or 3 years. In the future much will depend upon the way information is put at the disposal of industry. Very little is known as to how the Russians handle this problem. The United States is now preparing a law that will make information, as well as fissile material, available to her own industry. This is certainly a step in the right direction, and we can expect a vigorous development.

In Britain there is every hope that the new Atomic Energy Corporation is going to take industry into its confidence. Unfortunately, there does not seem to be much hope of the really close collaboration between this country and America which is long overdue. Had the United States not broken off the wartime collaboration with Britain about 10 years ago—again on account of a mistaken idea of "security"—it is very likely that both countries would now be much further on. As it is, both have to rely on their own efforts. What are the chances for us?

Britain has without doubt sufficient scientific and technologic potentialities to compete in the atomic power markets; the achievements of our atomic energy project with its relatively restricted means are certainly admirable. However, large-scale developments will need very much more technologic and scientific manpower than we have now, and no serious steps are yet being taken to remedy our shortcomings. I do not have the space to go into details, but I would like to refer the reader to my article on "The shortage of scientific manpower" which appeared in *The Financial Times* survey of British industry, 1954.

Why is so little being done in this all-important matter? It is said that the sums needed to modernize our technologic education and to create a healthy stock of science teachers cannot be made available. This, of course, is simply not true. Although it is often professed by V.I.P.'s in after-dinner speeches that in the world of today the future depends on science, one has

only to have a look at the way the country's money is spent to realize that this is mere lip service. Nobody can really uphold that a cut of, say, 1 percent in our defense expenditure would be of any great consequence—while these £15m per year would *double* the sums available to science and technology in the universities and the Department of Scientific and Industrial Research. Such a switch would increase our defense potential, as well as our chances for industrial survival, infinitely more than the damage due to the small reduction in the number of conventional weapons, which anyway will most probably be obsolete before they are ready.

These figures show clearly that the fact that this country must depend on its scientific and technologic manpower has not yet sunk in. This may be because the general public—certainly in this country—is not really science-minded. How often do we see people snobbishly dismissing all scientists and engineers as "narrow specialists," even though they themselves do not know the difference between science and gadgeteering. They do not realize that it is *their* narrow outlook which is an essential cause of our deficiences.

To sum up: It seems that the West has not yet learned to think in terms of the real values of this scientific age. The most important of these realities is the quality and quantity of scientific and technologic manpower. The Americans seem to be too blinded by their preoccupation with spy hunting to see that they are doing incalculable harm to their own scientists and that they are in grave danger of being overtaken by the Russians by quite legitimate means.

We in this country are fortunately free from the spy hysteria, but our share in the weapons project is anyway no more than that of a junior partner. On the other hand, the peaceful applications of atomic energy are bound to become essential for our future and here again the scientific manpower question is paramount. The facts are there for everyone who wants to see, but a deep paralysis seems to prevent us from doing what is necessary.

We are used to hearing Western papers loudly expressing contempt of the Communist countries, but this is neither sufficient nor even essential. We must *do better* than they, otherwise future historians may well be tempted to pass the famous verdict also on our generation: "Deus quos vult perdere, dementat prius."

News and Notes

International Weights and Measures, 1954

Continuing a series begun in 1889, the Tenth General Conference on Weights and Measures was held in Paris and Sèvres, France, 5 to 14 Oct. Of the 35 countries that belong to the international organization, 32 appointed delegates or observers, the total number being more than 70. As representatives of the United States, the Department of State appointed Allen V. Astin, director of the National Bureau of Standards, and E. C. Crittenden, consultant to the NBS.

These general conferences, which are convened at 61-yr intervals, exercise general authority over a permanent international committee of 18 members, which meets biennially. The committee is responsible for directing all projects in metrology that the member-countries decide to undertake jointly, including the preservation of the international metric standards and other activities of the International Bureau of Weights and Measures. The Bureau is housed at Sèvres in the Pavillon de Breteuil, an ancient residence designated as international territory. The International Bureau has a staff of about 16 persons. Besides providing a depository for international standards, it carries on important researches on many metrological problems, calibrates standards for other laboratories, both national and privately owned, and serves as a permanent secretariat for the international committee and the General Conferences on Weights and Measures.

Problems of measurement have become so diverse that no single small group of men can deal with them. Consequently to assist the International Committee on Weights and Measures in special fields, four advisory committees have been set up, each consisting of representatives of seven or eight national laboratories and some experts selected individually from smaller countries. The present advisory committees cover measurements and standards in electricity, in photometry, and in thermometry and the project for a new definition of the meter.

Many countries that belong to the international weights and measures organization do not have representatives in the permanent committees. Consequently one of the purposes served by each general conference is to inform member-countries of the progress made during the preceding 6-yr interval. The conferences are called upon to make decisions only on matters of principle or on changes of policy or practice.

Current work of the International Bureau was reported to the conference by Charles Volet, director of that Bureau, and various members of the Bureau's staff. It included comparisons of electric and photometric standards from all the larger countries, showing a very satisfactory degree of uniformity in the new electric units as adopted in 1948 and good progress toward uniformity of photometric measurements on all types of lamps. Comparisons of end-gages calibrated at various national laboratories by means of light-waves indicated that such calibrations are now sufficiently precise to meet the ordinary needs of in-

dustry but that the measurements would not be fully satisfactory for the establishment of basic standards, because the results obtained in different countries might differ by as much as 0.05 μ on a 100-mm gage, that is, 5 parts in 10 million. Further research is needed to determine the causes of these discrepancies.

In many physical measurements the force of gravity at the particular location must be known or assumed. The International Bureau therefore has in progress a determination of that force at Sèvres. Preliminary results reported to the conference indicate that the "Potsdam" basis for values of gravity, which has been generally used for half a century, is too large by 24 parts in a million. This agrees rather closely with determinations made at the National Bureau of Standards and the British National Physical Laboratory. However, additional determinations are under way in other laboratories. Consequently the international committee, following a recommendation of its Advisory Committee on Thermometry, agreed that values of the force of gravity involved in the determination of atmospheric pressures should conform to the classical Potsdam system until the international committee approves a change.

The International Bureau also reported the results of a recalibration of national kilogram standards completed since the Ninth General Conference in 1948. Of 24 standards originally certified in 1889, two showed no perceptible change, 14 had slight apparent increases in mass, and 8 showed small losses, the largest loss being 0.06 mg, or 6 parts in 100 million. Kilogram No. 20, which belongs to the United States, appeared to have increased by 2 parts in 100 million between 1889 and 1948; but if this was a real change, nine-tenths of it occurred before 1937, when the last previous comparison was made. The weighings of 1889 were not sufficiently precise to make it certain that any change has occurred in any of the national standards except one.

An intercomparison of national and international meter bars is scheduled to begin in 1955, and on this account special attention was directed to the possibility of increasing the precision of observations by ruling new lines to replace the original ones on the bars distributed in 1889. It is claimed that the lines can now be made so much better that the uncertainty of calibrations can be reduced by a factor of 10. Additional lines can be also be ruled to give a length of 1 m when the bar is at 20° instead of 0°C. Some countries have expressed a desire to have their meter standards reengraved to gain these advantages.

On the project to redefine the meter unit by basing it on wavelengths of light in a spectral line given by some single isotope, definite progress was reported. The Advisory Committee on Definition of the Meter, at a meeting in Sept. 1953, recommended that when a new definition is adopted it shall be expressed in terms of a wavelength in vacuum, derived from the presently accepted wavelength of the red cadmium line in air under standard conditions. The conversion from air to vacuum wavelengths is to be made in accordance with a formula for the dispersion of normal air adopted in 1952 by a Commission on Spectroscopy recognized as the best authority in this field. The international committee approved this procedure for developing the new definition, but the actual adoption of a definition was not possible because four different isotopes have been proposed as sources of light suitable for this purpose. Several years ago W. F. Meggers of the National Bureau of Standards proposed that the wavelength of the green line of mercury of mass number 198 be adopted. Workers at the German Physikalisch-Technische Bundesanstalt have advocated the use of a line in the spectrum of krypton 86 and, this year, have added xenon 136 as another possibility. Reports from the Russian Institute of Metrology have favored the retention of cadmium, using, however, cadmium 114 instead of the natural metal. The British National Physical Laboratory and the Canadian National Research Council Laboratory have studied some of these possibilities, but more information concerning the spectral lines of the isotopes, the types of lamps to be used, and other operating conditions is needed to give a basis for choice of a particular line. Consequently the conference, while recognizing the progress made, urged the laboratories to expedite their work on monochromatic radiations in order that the Eleventh General Conference may reach a decision on the problem.

The question of defining a unit of time more constant in value than the mean solar second as now determined by current astronomical observations was brought up by a resolution adopted by the International Union of Astronomy in 1952. The astronomers point out that the length of the mean solar day has varied by as much as 1 part in 10 million during the period from 1870 to 1950, and there is no assurance that even larger variations will not occur. Consequently the union recommended that for highly precise data (such as the frequencies assigned for some radio signals) the *second* be taken as a fraction of a single specified year. The formal resolution, however, referred to a "sidereal" year when it should have said "tropical" year. Consequently the general conference did not consider it advisable to act on the recommendation. Instead it authorized the international committee to decide the matter without waiting until another general conference convenes. The second will presumably be defined as "the fraction 1/31,556,925.975 of the tropical year 1900.0."

In accordance with a recommendation of the Advisory Committee on Thermometry, the conference adopted a new definition of the thermodynamic, or absolute, scale of temperature by assigning the value of 273.16°K for the triple point of water as the sole fixed fundamental point of the scale. This method of defining the scale has been advocated in recent years by W. F. Giauque of the University of California but was originally suggested a century ago by Lord Kelvin. Furthermore, any changes in assigned temperatures resulting from the change in definition of the scale are not likely to be greater than the uncertainty

of present measures. The name *Kelvin* is therefore retained.

In response to a request from the International Organization for Standardization for the establishment of a standard value for normal atmospheric pressure, the conference announced that the value adopted by the Ninth General Conference in the definition of the International Temperature Scale should be accepted for all purposes. It is 1,013,250 dynes/cm², or, in the mks system, 101,325 newtons/m².

A proposal for the establishment of a system of practical units for use by all countries submitted by the French Government in 1948 gave rise to such diverse comments that the international committee was unable to prepare a generally acceptable revision. By a divided vote on some details, the conference decided that as a basis for such a system the following units should be adopted: for length, the *meter*; for mass, the *kilogram*; for time, the *second*; for electric current, the *ampere*; for thermodynamic temperature, the *degree Kelvin*; for luminous intensity, the *candela*.

With regard to finances it was reported that, following a request made by the Ninth General Conference, 21 countries have made special gifts totaling about 79,000 gold francs ($25,800) for the improvement of the plant and equipment of the International Bureau. Although the United States Government has made no special cash gift in response to this request, it may be recalled that private American agencies have in the past given material assistance to the International Bureau. In particular the Rockefeller Foundation gave funds for the enlargement of the Bureau laboratory to provide room for work on electric standards.

By action of the international committee, valid because delegates of no country objected when the decision was reported to the conference, the basic budget (contributions of countries that adhered to the Convention of the Meter before 1921) was increased from 175,000 gold francs to 300,000. On a corresponding scale eight countries that have adhered more recently will pay 55,000 gold francs, making the total of dues for the support of the International Bureau 355,000 gold francs ($116,000) per year.

As a final act the general conference elected members of the international committee to bring the membership up to the total of 18, as provided by the Convention of the Meter. Five members elected in 1948 or earlier remain. These are from Argentina, Italy, Roumania, Sweden, and Yugoslavia. Eight members elected provisionally by the international committee between 1948 and 1954 were confirmed. These members are from Canada, Czechoslovakia, France, Germany, Japan, the Netherlands, Spain, and the U.S.S.R. The remaining five vacancies were filled by electing members from Australia, Austria, Finland, the United Kingdom of Great Britain and Northern Ireland, and the United States of America. Allen V. Astin is the new American member succeeding E. C. Crittenden, who resigned at the close of the conference. At a meeting after the conference, the international committee elected as its president A. Danjon, director of the Observatory of Paris; as vice-president F. Vieweg, president of the German Physikalisch-Technische Bundesanstalt; as secretary, G. Cassinis, rector of the Polytechnic School of Milan, Italy.

E. C. Crittenden

National Bureau of Standards, Washington, 25, D.C.

Science News

The following editorial on the loyalty case of **John F. Peters**, professor of medicine at Yale University, appeared in the 29 Nov. issue of the *Washington Post and Times Herald*.

In consenting recently to review the case of Dr. John F. Peters, the Supreme Court accepted an opportunity to come back to the difficult issues which it left unresolved in the *Bailey* case two years ago. The issue in simple terms is whether the Government, by reliance on unsworn statements by anonymous informants, can declare employes in nonsensitive positions to be disloyal and disqualify them from Government service.

Dorothy Bailey was dismissed from the Government in 1949 under such circumstances. The Loyalty Review Board, after a hearing in which all the testimony was favorable to her, and in admitted reliance on informers whose identity was unknown to the board as well as to Miss Bailey, recommended her dismissal because of doubts as to her loyalty. A Federal District Court denied her plea that this procedure violated her constitutional rights and the intent of the loyalty order. The Court of Appeals affirmed by a division of 2 to 1; the Supreme Court divided 4 to 4 (Mr. Justice Clark having disqualified himself), with the result that the lower court decision was sustained.

Dr. Peters is an eminent physician and the senior professor of medicine at Yale University. For several years, prior to 1951, he served as a special consultant to the Public Health Service, advising the Surgeon General on proposals to grant Federal assistance to medical research projects—work which involved no access to confidential or strategic information. Charges were lodged against him in 1949 by unknown persons; but he was promptly cleared by the agency loyalty board. The charges were brought up again in 1951; and after a hearing he was cleared once more. In 1953, however, he was called before the Loyalty Review Board for a post-audit; and the board concluded there was a "reasonable doubt" as to his loyalty.

In the hearing before the board, Dr. Peters affirmed his loyalty to the United States and answered all questions under oath. Among the witnesses who appeared, also under oath, to assert their belief in his loyalty were Charles W. Seymour, former president of Yale; Judge Charles E. Clark of the Second Circuit Court of Appeals, and C. M. H. Long, former dean of the Yale Medical School. The only evidence against him came at second hand from informants whose testimony was not taken under oath and whose identity, with a single exception, was unknown to the board. Dr. Peters, of course, had no opportunity

to cross-examine them and no real means of refuting their allegations, since he could not know precisely what they were.

Few Americans will dispute the need for a fair and efficient loyalty check system in Government. The question is whether the procedures in the Peters case served to impose a kind of punishment without due process. It will be constructive for the Supreme Court to examine these procedures and say definitely whether they comport with the Constitution.

The American Physiological Society passed this resolution at its autumn meeting in Madison Wis.

Whereas The American Physiological Society was founded to facilitate the advancement and utilization of the physiological sciences, and is therefore deeply concerned about practices which might obstruct the services of physiologists to the public, and

Whereas the present state of international tension has brought about in the United States of America a legitimate concern for the security of our country, which has, however, unfortunately led to the institution of practices which are in our opinion both improper and unwise; and which have resulted in the denial or withdrawal of grant-in-aid funds to support the unclassified researches of investigators suspected but not convicted of subversive or disloyal acts.

Now therefore be it resolved that The American Physiological Society publicly record its unqualified opposition to any abridgment of the basic tenets of the United States Constitution and its amendments, and the American principle of maintaining that a person is innocent until proven guilty of a specific offense; and we condemn any invasion of the American community by principles and practices which are characteristic of authoritarian, dictatorial governments, and urge that a firm stand be made against the introduction of punitive devices to circumvent the constitutional rights of United States citizens; and we call special attention to the fact that the whole nation loses when a scientist is improperly and unnecessarily prevented from contributing to new knowledge; and

It is further resolved that this Society appeal to the proper authorities to conduct our national government so as to preserve the principle of innocence of citizens until guilt is proven, and to make adequate provision for appeal to an impartial body by those scientists denied financial support, to the end that the talents of worthy scientists will be utilized in the promotion of knowledge in the public interest, which is best served by the preservation of the principles of justice and tolerance without which any struggle against authoritarianism becomes meaningless, and

It is further resolved that nothing in this document is intended to advocate protection for those guilty of disloyal or subversive acts against the United States.

R. S. Satoskar and R. A. Lewis of Seth G. S. Medical College, Bombay, India, report in the current issue of *Antibiotics and Chemotherapy* (vol. 4, No. 11) that there is evidence that **terramycin raises blood protein** when given to a person on a low-protein diet. The investigators analyzed the effect of small daily doses of terramycin and vitamin B_{12} on the blood protein make-up of 14 of their students. For control purposes the students were divided into three groups. One group received only the antibiotic, another the vitamin supplement alone, and the third, the two in combination.

At the end of 2 mo all students receiving terramycin, either alone or in combination with vitamin B_{12}, had increased blood proteins. The group receiving the vitamin alone showed little change. From these observations, Satoskar and Lewis believe that terramycin may increase the body's ability to use the proteins in the diet by changing the bacterial population in the intestines.

Albert André Nast, an obstetrician in Chelles, a Paris suburb, recently delivered his 4500th baby, his **2000th delivery since he became blind** 24 yr ago. He has so developed his sense of touch that he regularly performs surgery.

Two types of rare **"living insect fossils"** from the Ice Age have been discovered in Death Valley in a pond near Saratoga Springs by John Belkin and William McDonald of the department of entomology at the University of California at Los Angeles. One group, *Corethrella lanceana*, is evolutionally midway between gnats and true mosquitoes. This species is different enough to suggest a distinct subspecies.

The other find is a true mosquito. Known as *Uranotaena anhydor*, it is related to a type found in Texas. It is thought to feed on frogs. Both populations of insects apparently have been isolated in the desert area since the end of the last glacial period.

In the same area Carl L. Hubbs of the Scripps Institution of Oceanography found a "living fish fossil." This was the desert pupfish that is thought to have been isolated in the area for 11,000 yr.

Mucic acid has been isolated for the first time from fresh fruit. E. F. L. J. Anet and T. M. Reynolds of Homebush, N.S.W., Australia, report the achievement in the 13 Nov. issue of *Nature*. The only other known natural occurrences of the acid are in putrified blood and in sugar beet juice. From almost 4½ lb of ripe peaches or pears only a trace, approximately 1/10 gr, was obtained. The method of isolation makes it almost certain that the acid, a white crystalline oxidation product of milk sugar, was present in the fruit in a natural state. Mucic acid is a substitute for cream of tartar in baking powder.

New Jersey antivivisectionists are **opposing establishment of any medical school** or dental college in the state, although the state has more than 4 million residents and not a single medical school.

A major expansion and reorganization of the **commissioned reserve of the Public Health Service,** Department of Health, Education, and Welfare, as a national defense measure has been announced. The USPHS expects to commission an additional 2000 re-

serve officers by 30 June 1955, and present plans call for the commissioning of another 3000 officers during 1955–56. In addition to building up the commissioned reserve to emergency strength, USPHS is stepping up research in disaster health problems and is developing a program to reinforce state and local health departments in time of national crisis.

C. V. Raman, professor of physics at the Indian Institute of Science, and director of the Raman Research Institute, both in Bangalore, India, has reported the discovery of a new kind of **gypsum that is doubly refractive.** Raman received the Nobel prize in 1930.

Russia is attempting to establish A. M. Butlerov, a 19th century Russian chemist, as the **father of organic chemistry** in the same manner that biologist T. D. Lysenko was once idolatrized. An interesting by-product of this attempt is the simultaneous effort to discredit Linus Pauling, 1954 winner of the Nobel prize for chemistry, whose work is related to that of Butlerov.

In a recent report to the American Chemical Society's *Journal of Chemical Education,* I. Moyer Hunsberger of Antioch College stated that the criticisms of Pauling's work and the elevation of Butlerov are an "extremely obvious exaggeration of Butlerov's contributions to organic chemistry." Hunsberger also reported that the great majority of Russian papers extolling the work of Butlerov and other Russians in the field of organic chemistry inevitably include "torrents of invective" against Western science in general and Pauling in particular. Russia believes that Pauling has contributed theories to organic chemistry that directly oppose communistic philosophy, and are therefore "an example of world outlooks hostile to the Marxist view."

R. A. Hefner, professor of zoology at Miami University, Oxford, Ohio, has reported that a student, Alan Linn, discovered more than 20 **multilimbed bullfrogs** in a pond in southern Ohio. Multiple limbs have been induced on frogs artificially, but in nature such duplications are freaks. The frogs found vary in abnormality from one extra hind leg below the knee to as many as six hind legs.

A subcommittee of the House Committee on Education and Labor is assembling data on **Federal support of medical research** in teaching institutions. The study is part of its general investigation of Government activities in relation to education at all levels. At the request of Rep. Ralph W. Gwinn (R., NY), subcommittee chairman, Federal agencies are furnishing great quantities of information bearing on their grants-in-aid, teaching assistance, and graduate education programs. The Gwinn subcommittee has conducted hearings intermittently since September. These were concluded on 7 Dec. and a final report is to be published soon.

Scientists in the News

Grant L. Rasmussen has been appointed chief of the section on functional neuroanatomy in the laboratory of neuroanatomical sciences, National Institute of Neurological Diseases and Blindness, Bethesda, Md. He formerly was professor of anatomy, in charge of neuroanatomy, at the Medical School of the University of Buffalo. He is well known for studies of the central auditory mechanisms of the brain.

Carl S. Hallauer, executive vice president of Bausch and Lomb Optical Co., Rochester, N.Y., has been elected president of the 101-yr-old firm, the largest integrated optical plant in the world. He began his business career as a newsboy when orphaned at the age of nine.

Paul C. Bucy, professor of neurology and neurological surgery at the University of Illinois since 1941, has joined the faculty of Northwestern University's medical school as professor of surgery.

A research scientist and an electronics engineer were awarded the first National Electronics Conference award at the tenth anniversary session of the conference held recently in Chicago. Recipients of the $250 award were **E. D. McArthur,** manager of the electron tube section at the G.E. Research Laboratory, Schenectady, N.Y., and **E. F. Peterson,** manager of marketing for the G.E. radio and television department in Syracuse, N.Y. They were honored for their paper entitled "The lighthouse tube; a pioneer ultra-high-frequency development" presented at the first NEC conference in 1944.

The new award will be presented annually to "the author or authors of a paper presented at a previous conference which introduced developments of a new and revolutionary character capable of significantly influencing an electronic field or of opening an avenue to a major field of electronic science of application."

Pierre Grabar, director of the biophysics section of the Pasteur Institute, Paris, has accepted appointment as a senior fellow in the James W. McLaughlin Fellowship Program in Infectious Diseases and Immunity at the University of Texas Medical Branch, Galveston. He will work in the tissue culture laboratory and in the tissue metabolism laboratory.

Another visitor from abroad is **Bingt Yohanson,** professor of plastic surgery, University of Stockholm, who is at the Medical Branch to survey the methods being used for the treatment of severe burns.

The Bendix Aviation Corp. has announced the appointments of **A. P. Fontaine** as director of engineering and of **A. C. Hall** as general manager of the Research Laboratories. Fontaine, who will also have jurisdiction over the laboratories of the corporation, will supervise an engineering program that during the past year expended $70,000,000 and used the services of a staff of more than 7000 persons. Prior to his present ap-

pointment Fontaine helped direct expanded operations in aircraft control, navigation and instrument equipment, electron tubes, ignition systems, meteorological instruments, precision electric units, and other products at six of the 24 manufacturing divisions of Bendix.

Hall, previously an associate professor at MIT, has been serving as technical director of the Bendix Research Laboratories. Since he joined the firm, he has directed development work for missile guidance systems, hydraulic control components, digital and analog computers, automatically controlled machine tools, and special instruments for process controls.

Carl Binger has been appointed lecturer in psychiatry at the Harvard Medical School and consulting visiting psychiatrist at Massachusetts General Hospital. Binger, who is particularly interested in the problems of mental health in relation to education, has also been appointed psychiatric consultant to the medical staff of Radcliffe College. He will participate in the Radcliffe Seminars, an adult education program at the graduate level offered to women in Greater Boston.

Binger, editor-in-chief of *Psychosomatic Medicine*, was formerly associated with the Rockefeller Institute for Medical Research, and until recently practised psychiatry in New York, where he was on the faculty of the Cornell University Medical College and on the visiting staff of New York Hospital.

The Browder J. Thompson memorial prize for 1955 has been awarded by the Institute of Radio Engineers to **Blanchard D. Smith, Jr.**, of Melpar, Inc., Alexandria, Va., for his paper "Coding by feedback methods," which appeared in the Aug. 1953 issue of the *Proceedings of the I.R.E.* The award is made annually to an author under 30 yr of age at date of submission of manuscript for a paper, recently published by the IRE, that constitutes the best combination of technical contribution and presentation of the subject. Smith is a consulting project engineer on electronic research and development projects.

William A. Hunt, chairman of Northwestern University's psychology department, delivered the three Thomas W. Salmon lectures before the New York Academy of Medicine early this month. He discussed the role of the clinical psychologist in the study and treatment of mental illness. This was the first time since the establishment of the lectureship in 1932 that the honor was extended to a psychologist.

Morris M. Leighton, emeritus chief of the Illinois State Geological Survey, was an official guest of the Board of Natural Resources and Conservation, State of Illinois, at a dinner given in his honor on 20 Oct. to commemorate his completion of 31 yr as chief of the survey. During his tenure, Leighton extended the geological research of the survey along fundamental and applied lines, added geochemistry and mineral economics as substantial sections of the organization, gradually increased the full-time staff from 15 to 125 persons, and was instrumental in interesting the General Assembly and the Governor of Illinois in appropriating nearly $5 million for the construction and equipment of the National Resources Building for the research work of the Geological Survey and the Natural History Survey. The research laboratories of the Geological Survey number more than 40 and the biennial budget exceeds $1,600,000.

With the combined staffs of the department of geology of the University of Illinois and of the Geological Survey, Urbana has become one of the largest and most active geologic research centers in the country. On 1 July Leighton retired from his administrative duties; he has resumed his research on the Pleistocene geology of Illinois. His successor is **John C. Frye**, former state geologist of Kansas and professor of geology at the University of Kansas.

Ernest O. Lawrence, director of the University of California Radiation Laboratory, has been awarded the 1954 medal of the American Cancer Society for his "distinguished contribution to cancer control." He was cited for opening up new fields of cancer research through his development of the cyclotron.

Peter Brian Medawar, Jodrell professor of zoology and comparative anatomy at the University of London, gave the annual New York University Post-Graduate Medical School Sigmund Pollitzer lecture at the NYU–Bellevue Medical Center on 15 Nov. He spoke on "Skin transplantation and the homograft problem."

Clyde H. Bailey, retired dean of the University of Minnesota's Institute of Agriculture, has been presented the 1954 Gamma Sigma Delta national award for distinguished service to agriculture. The honor society of agriculture recognizes one outstanding agriculturist each year. Bailey retired on 30 Dec. 1952 after more than 40 yr of service as a teacher, biochemist, and administrator—all at the University of Minnesota, the institution he enrolled in at the age of 13. His research resulted in many advancements in cereal chemistry and food technology. He devised many methods of flour quality testing and is recognized for them throughout the world. His work on grain storage chemistry and his ability to develop new research devices have also won him wide recognition.

He helped establish the American Association of Cereal Chemistry and is author of three books and more than 300 scientific and technical articles. A member of the American Association of Cereal Chemists, he has been its president and editor and has served on many of its committees.

Maurice G. Kelliher, formerly of the Mullard Research Laboratories at Surrey, England, and an engineer whose field is linear accelerator design and construction, has joined the staff of High Voltage Engineering Corp., New York. The company has built, in cooperation with Stanford University, a 50-Mev "li-

nace" for the Atomic Energy Commission's Argonne Cancer Research Hospital in Chicago and has just completed the first of a new line of small, high-power linear accelerators to operate in the 4 to 8-million-volt range for use in radiography, industrial processing, and medical research.

William D. Robinson, professor of medicine at the University of Michigan Medical School, has been appointed editor of the *Journal of Laboratory and Clinical Medicine,* the official organ of the Central Society for Clinical Research; **William H. Beierwaltes,** associate professor of medicine at Michigan, is the new associate editor. They replace **Clayton G. Loosli,** professor of medicine, University of Chicago School of Medicine, who has held the editorship for the past 6 yr, and his colleague Robert H. Ebert, associate professor of medicine, who has been associate editor for 1½ yr. After 1 Jan. manuscripts submitted for possible publication in the *Journal* should be sent to Dr. Robinson.

Alfred Weissler, former chief of the Washington office and of the chemistry branch of the Office of Ordnance Research, U.S. Army, has joined the research grants branch of the National Cancer Institute, Bethesda, Md.

Necrology

Tadeusz Banachiewicz, 72, astronomer, mathematician, author, and director of the Krakow Astronomical Observatory, Krakow, Poland, late November; **Robert R. Chace,** 44, instructor in ophthalmology at Columbia University's College of Physicians and Surgeons, New York, 24 Nov.; **Edwin M. Chance,** 69, chemist, mining engineer, inventor, and president of United Engineers and Constructors, Philadelphia, Pa., 26 Nov.; **Enrico Fermi,** 53, pioneer nuclear physicist, Nobel prize winner, former associate director of the Los Alamos Laboratory, and distinguished service professor for nuclear studies at the University of Chicago, Chicago, Ill., 28 Nov.; **Winifred Hathaway,** 84, educator and associate director of the National Society for the Prevention of Blindness, New York, 1 Dec.

Leon Menzl, 71, consulting engineer for the sugar industry, Westport, Conn., 29 Nov.; **Jerome Mullane,** 73, retired horticulturist with the Boyce Thompson Institute for Plant Research, Yonkers, N.Y., 24 Nov.; **Herbert Osborn,** 98, professor emeritus of zoology and entomology at Ohio State University, Columbus, Ohio, 20 Sept.; **Edwin A. Stevens,** 72, marine engineer, specialist in propeller design, and author, Hoboken, N.J., 1 Dec.; **Joseph W. Stewart,** 54, chief mechanical designing engineer for the Cochrane Corporation, Philadelphia, Pa., 24 Nov.; **Wallace R. Turnbull,** 84, mechanical and electrical engineer, pioneer in aeronautical development, and inventor of the variable-pitch propeller, St. John, N.B., Canada, 26 Nov.

Meetings

Alcoholism and narcotic addiction will be reviewed in the 30th annual Hermann M. Biggs memorial lecture at the New York Academy of Medicine, 3 Feb. The lecture will be in two parts. Giorgio Lolli, director of the Silkworth Memorial Service at Knickerbocker Hospital in New York, will speak on "Alcoholism as a medical problem." Lolli is also director of the Yale Plan Clinic at Yale University, and is consultant on professional services to the Connecticut Commission on Alcoholism. The second speaker, Harris Isbell, director of the Addiction Research Center at the U.S. Public Health Service Hospital, Lexington, Ky., will lecture on the "Medical aspects of drug addiction."

The 11th annual **Conference on Protein Metabolism,** sponsored by the Bureau of Biological Research of Rutgers University, will be held in New Brunswick, 28–29 Jan. 1955. General subject of the conference will be *Some Physiological Aspects and Consequences of Parasitism.* Reports will be given by William Trager, Clark P. Read, James W. Moulder, Ernest Bueding, W. H. Taliaferro, and Leslie A. Stauber on cultivation of intracellular parasites, intestinal physiology and the host-parasite relationship, protein metabolism of intracellular parasites, glycolytic enzymes of schistosomes, antibody formation, and leishmaniasis and metabolism of the host. The conference is open to all registrants. Reservation blanks may be obtained from Prof. William H. Cole, Rutgers University, New Brunswick, N.J.

A group of approximately 30 investigators and clinicians who are prominent in the development of artificial kidneys, artificial heart-lung machines, and similar biomechanical equipment have organized a society, the **American Society for Artificial Internal Organs,** for the purpose of exchanging information and of stimulating developments in this field. The first meeting of this group will be held in conjunction with the meeting of the American Medical Association, 4–5 June 1955, in Atlantic City, N.J. Arrangements for a scientific program and for a dinner meeting are being made at this time. Information may be obtained from the acting secretary, Dr. Peter F. Salisbury, Institute for Medical Research, Cedars of Lebanon Hospital, 4751 Fountain, Los Angeles 29, Calif.

The annual meeting of the national **Association of Geology Teachers** is to be held in combination with the annual meeting of its East Central section at Columbus, Ohio, 28–29 Jan. 1955. The geology department at Ohio State University is acting as host and a local committee is making plans. There will be a tour through the research quarters of the Battelle Memorial Institute, which employs a large staff of geologists, and there will be visits to the U.S. Geological Survey Coal Laboratory and the Ohio division of the Geological Survey. Exhibits of teaching aids in geology are invited. The meetings will include a sym-

posium, *Geology on TV*, and a film and panel on "Increasing college enrollments: what will they mean to geology?" There will be a short business session, and at the annual banquet the 1954 Neil Miner award will be made and the president and retiring president, Leland Horberg and W. H. Shidler, will speak.

Available Fellowships and Awards

In recognition of the contributions to science of Selman A. Waksman, **the Waksman-Merck postdoctoral fellowship** in the natural sciences related to the fields of medicine and health has been established at Rutgers University by Merck and Co., Rahway, N.J. The fellowship is open to citizens of the United States or Canada who have received, or are about to receive, the Ph.D. or equivalent degree and are interested in further training and research experience in biochemistry, chemistry, entomology, microbiology, nutrition, physics, physiology, or zoology as related to medicine and health.

The award is $4000 for 1 yr, beginning 1 July 1955. *The closing date for receipt of applications is 10 Jan. 1955.* Application forms may be obtained from the Dean of the Graduate School, Rutgers University, New Brunswick, N.J.

Nominations are now being received by the American Pharmaceutical Association for the 1955 **Chilean Iodine Educational Bureau, Inc., award** recognizing outstanding research in the chemistry and pharmacy of iodine and its compounds as applied in pharmacy or medicine. The award consists of $1000 and a diploma setting forth the reasons for selection of the recipient. It may be presented each year at the annual meeting of the association.

Any member of the association may propose a nominee by submitting eight copies of each of the publications to be considered in the competition, a biographic sketch of the nominee including date of birth, and a list of his publications. Eight copies of the nomination must be submitted to Robert P. Fischelis, Secretary of the American Pharmaceutical Association, 2215 Constitution Ave. NW, Washington 7, D.C. To be eligible for the 1955 award, *nominations must be received on or before 1 Jan. 1955.*

The Institute of International Education, 1 E. 67th St., New York, has announced that the **University of Ceylon,** Peradeniya, is offering two fellowships to American graduate students for the 1955–56 academic year. Awards cover room, board, and tuition. Grantees should have funds to pay their own travel and incidental expenses. *Closing date for application is 15 Jan. 1955.*

The Ceylon fellowships offer Americans an opportunity to study a variety of subjects, including sociology. Male candidates under 35 yr of age are preferred. Other eligibility requirements are U.S. citizenship; a good academic record; good moral character, personality, and adaptability; a broad knowledge of the culture of the United States; and good health. Applicants should write to the institute's U.S. Student Department.

Applications are being received for the **Drummond fellowship for research in nutrition.** The value of the fellowship will be £900 per annum, to which may be added a grant for expenses of research not exceeding £50 per annum. In addition up to £90 may be paid for superannuation. The fellowship will normally be tenable for 2 yr. Full particulars can be obtained from the Honorary Secretary, Drummond Trust, University College London, Gower Street, London W.C.1. Completed application forms *must be received not later than 15 Jan. 1955.*

Grants and Fellowships Awarded

The Committee on Dentistry of the National Research Council has officially approved 10 dental research projects sponsored by the Research and Development Division of the Office of the Army Surgeon General. The period of approval is for 12 mo beginning 1 Dec.

University of Michigan. J. K. Avery. Development and growth of the human tooth.

University of Minnesota. W. D. Armstrong. Determination of microquantities of fluoride in biological materials.

Indiana University. H. G. Day. Fluorine in nutrition and dynamic state of teeth and bones.

Indiana University. R. B. Fischer. Physical structure of dental enamel and bones.

Indiana University. R. W. Phillips. Electrical and thermal conductivity of dental cements and restorative materials.

Medical College of Virginia. S. B. Kreshever. Effect of local irritants on oral tissues.

Tufts College Dental School. R. S. Manly. Synthetic dental plaques prepared from strains of oral microorganisms.

University of Illinois. M. B. Engel. Histochemical studies of dental tissue.

Harvard School of Dental Medicine. R. S. Seganaes and J. M. Shaw. Interrelations between the oral hard structures and their internal and external environments in health and disease.

New York University. O. R. Trauts. Apatites of dental enamel.

The National Foundation for Infantile Paralysis has recently awarded 127 scholarships and fellowships in the fields of physical therapy and occupational therapy and 66 scholarships in medical social work. In addition, the following awards were made.

Teaching fellowships

Yolanda Diaz, Hato Rey, Puerto Rico; div. of physical therapy, Stanford University, 18 mo.

Ronald A. Hershey, Los Angeles, Calif.; dept. of physical therapy, University of Southern California, 17½ mo.

V. Joyce Lim, Los Angeles, Calif.; dept. of physical therapy, University of Southern California, 12 mo.

Rachel Lee Nunley, Greenville, S. Car.; dept. of anatomy, Duke University, 15 mo.

Melvin A. Orser, Los Angeles, Calif.; dept. of physical therapy, University of Southern California, 12 mo.

Betty J. Sanders, Oklahoma City, Okla.; div. of physical therapy, Stanford University, 18 mo.

Sara M. Schoppenhorst, Kansas City, Kan.; div. of physical therapy, Stanford University, 14¾ mo.

E. Joan Turnquist, Salt Lake City, Utah; div. of physical therapy, Stanford University, 11½ mo.

Marian Williams, Stanford, Calif.; dept. of anatomy, Stanford University, 9½ mo (extension).

Shirley M. Bowing, Tacoma, Wash.; dept. of occupational therapy, University of Southern California, 8¾ mo.

Mailyn R. Fakler, Iowa City, Iowa; dept. of speech pathology, State University of Iowa, 14 mo.

Travel grants

Margaret O. Camp, Middletown, Conn.; observation and experience in centers in England, Denmark, France, Switzerland, Germany, Italy, Netherlands, Sweden, Norway, 3 mo.

Ruth Cook, San Francisco, Calif.; International Poliomyelitis Congress, Rome, and observation and study of facilities in clinics and hospitals in Switzerland and Southern Germany, 2 mo.

Ermine R. Duccini, Fair Oaks, Calif.; study of facilities in clinics and hospitals in Italy, 2 mo.

In the Laboratories

Ground was broken on 3 Nov. for the $750,000 Research-Laboratory Building at the **New York Botanical Garden.** The Garden's research program has been conducted under difficulties imposed by inadequate facilities in the basement of the Museum and Administration Building. The new structure, with microbiology, biochemistry, plant physiology, and plant pathology laboratories, will permit expansion of studies in antibiotics, plant nutrition, and plant growth of significance to man, and of studies of insect pests and plant diseases and their control.

When Honduras was hard hit by storm and flood this fall **Parke, Davis and Co.,** Detroit, donated 5000 doses of Chloromycetin and 5000 doses of Camoquin. The medicine was flown from the firm's branch at Colon, Panama, to health authorities at Tegucigalpa.

The new address of the **Armour Laboratories** general office is Kankakee, Ill. All executive and administrative personnel and equipment were transferred to the new Armour Pharmaceutical Center in early October.

The Naval Ordnance Development Award has been given for the second time to the **Applied Physics Laboratory of The Johns Hopkins University,** Silver Spring, Md. The laboratory, which is under the direction of R. E. Gibson, was cited for "continued outstanding scientific achievement since 1945, and in appreciation of exceptional service to Naval Ordnance Development."

Miscellaneous

A new periodical, ***Clinical Chemistry,*** official journal of the American Association of Clinical Chemists, will begin publication in January 1955. Designed to serve the clinical laboratory worker, the new journal will be devoted to the publication of original articles on all aspects of clinical chemistry. It will also supply the only central abstracting service covering the field. Establishment of the journal brings to fruition 5 yr of planning by the association. Material of utmost importance to clinical chemistry and to clinical laboratories previously scattered throughout scientific literature will now be available in a single source. It is hoped that the new journal will make a positive contribution to modern medical progress by shortening the time lag between new findings and their practical use in the laboratory.

Harold D. Appleton, Metropolitan Hospital, New York, and the present editor of *The Clinical Chemist,* has been named chairman of the editorial board of the new journal. The board will consist of Hugh J. McDonald, Loyola University, Chicago; Marschelle H. Power, Mayo Clinic, Rochester, Minn.; John G. Reinhold, University of Pennsylvania; Joseph I. Routh, University of Iowa; Harry Sobotka, Mt. Sinai Hospital, New York; and Warren Sperry, N.Y. Psychiatric Institute, New York.

Papers submitted for publication should be addressed to Harold D. Appleton, Editor, *Clinical Chemistry,* Box 123, Lenox Hill Station, New York 21. Papers from European scientists may be sent directly to the New York address or to the publication's foreign editors: Dr. J. C. M. Verschure, Emmalaan 41, Utrecht, The Netherlands; and Prof. E. J. King, Postgraduate Medical School, University of London, London.

Clinical Chemistry will be published bimonthly by Paul B. Hoeber, Inc., 49 E. 33rd St., New York 16. The annual subscription price will be $8 in the U.S.A. and countries of the Pan American Union, $8.50 in Canada, and $9 elsewhere.

To assist scientists engaged in studies on the **chemotherapy of cancer,** a program for wide exchange of information in this field of medical research has been established by the Committee on Chemotherapy of the National Advisory Cancer Council in cooperation with the National Cancer Institute, the American Cancer Society, and the Damon Runyon Fund. All investigators interested in cancer chemotherapy are invited to take part in the program. Chairman of the committee is Sidney Farber, director of the Children's Cancer Research Center, Boston.

A variety of activities will be developed through the program. Among them are (i) issuance of a periodic compilation of informal reports on current research in cancer chemotherapy; (ii) formal conferences and symposiums on cancer chemotherapy; (iii) compilation and issuance of a bibliography of cancer chemotherapy literature covering the period from 1946 through 1954; (iv) provision of opportunities for individuals and small groups to meet informally in various parts of the country for discussions of interinstitutional studies, of standards for evaluating chemical agents, of difficulties in this research area, of potentially useful agents, and of other topics the conferees consider pertinent.

In addition, the committee plans to bring to the attention of investigators chemical agents that may be of interest to them and to assist them in obtaining the chemicals in sufficient quantity for evaluation. Investigators who wish to take part in any of the activities of the program are invited to write to Dr. Gordon Seger, Secretary, Cancer Chemotherapy Committee, National Cancer Institute, Bethesda 14, Md.

Book Reviews

Administrative Medicine. Transactions of the first conference, 9–11 Mar. 1953. George S. Stevenson, Ed. Josiah Macy, Jr., Foundation, New York, 1953. 176 pp. Illus. $3.

This is a report of the first of five annual conferences on administrative medicine conducted under the auspices of the Josiah Macy, Jr., Foundation. These conferences are designed to foster joint planning for the solution of major problems in administrative medicine by providing informal exchange of ideas and facts among individuals of varied background and training related to this field.

This particular conference was devoted to the broadening of medical care beyond the immediate treatment of disease by developing an awareness in the health professions of the many related important factors in the management of disease and the preservation of health. These included preventive, economic, political, environmental, and genetic influences on the cause, evolution, and termination of disease and the provision of medical care. Many important points were made.

Spirited discussion centered around the relationship of the social sciences to medical care and medical education, stimulated by participants representing widely divergent points of view. On the one hand, it was recommended that the concepts of social science be recognized as important determining factors in medical administration. It was further proposed that the "social science disciplines" be a major focal point in educational programs for the health professions. In contrast, it was also argued that these were only common-sense measures and that, in particular, the medical curriculum should be limited to more important matters, such as the basic sciences and clinical medicine based on pathologic physiology. Curiously enough, no mention was made of the need for distinguishing between established facts and undocumented ideas in the social sciences. In my opinion, much of the controversy would disappear if representatives of the social sciences would clearly distinguish in their fields, as has been done in the physical and biological sciences, the concepts deduced from scattered individual observations from principles induced by means of the scientific method.

This report makes interesting reading. The editor has preserved the informal and spontaneous flavor of the conference in these transactions. As he will in the case of reports of all informal conferences, however, the casual reader is likely to find a need for guidance. This could be provided *post hoc* by appending a list of appropriate references where documentation is possible. The lack of such documentation recommends this book primarily to the informed reader.

DAVID D. RUTSTEIN

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Contributions to American Anthropology and History. vol. XI, Nos. 52–56. Carnegie Institution of Washington, Washington, D.C., 1952. 236 pp. Illus. + plates. Cloth, $7.50; paper, $6.75.

Of the five papers composing this generously illustrated volume, the one entitled "Mound E-III-3, Kaminaljuyu, Guatemala," by Edwin M. Shook and Alfred V. Kidder, has the broadest interpretative significance. The paper contains a detailed description of the excavation of a single mound in a large archeological site. So technical is the presentation that even the authors warn the nonspecialist reader to skip to the brief summary. Nevertheless, an important general point is brought out in the discussion. As evidenced by this mound containing two elaborate tombs, a stage of development—social, religious, and technologic—must have been attained at an earlier time than hitherto believed. The mound belongs to the period labeled Archaic, yet the degree of cultural advance is closely comparable to that of the Classic period. In conclusion, the authors suggest that if leadership in the development of the social structure typical of Classic Mesoamerica was assumed by any single pre-Classic people, those responsible for the enormous mounds, of which E-III-3 is one, might well have been that people.

The object of the paper by Ralph L. Roys, "Conquest sites and the subsequent destruction of Maya architecture in the interior of northern Yucatan," is to furnish a general picture of the towns and buildings both contemporary and abandoned which the Spaniards found in the more thickly populated regions of the area. Additional evidence is given, "not only that a large number of the towns in northern Yucatan are located at their pre-Spanish sites, but that the present churches and plazas are situated at the ceremonial centers of the old towns."

The ball game of the ancient Maya attracts modern interest because it was played with a heavy solid rubber ball of native manufacture, because it was a team game by means of which towns and localities competed, and because it was played by both amateurs and professionals. The study "The ball courts at Copan," by Gustav Strömsvik, includes comparative material on ball courts from four other Maya centers in the vicinity of the key site. The results indicate that Copan is the oldest court yet discovered, and the author concludes that the origin of the game perhaps antedates formal architecture in Mesoamerica and that the complex very probably spread from a common point of origin.

In "Pottery from Chipoc, Alta Verapaz, Guatemala," Robert E. Smith establishes what at present appears to be "the only true ceramic phase known in that region." As in the other papers, many questions are raised and the necessity for much more extensive work is emphasized.

The contribution by Howell Williams, "Geological observations on the ancient human footprints near Managua, Nicaragua," differs from the other papers in that it is a critical and definitive review of all the evidence to date bearing on the fascinating but complicated problem of deciding when the footprints were made. After the footprints came to the attention of the scientific world in the latter part of the 19th century, a controversy raged, with many taking the side of the archeologist Flint, who claimed that they "were at least 50,000 years old, and might be 200,000." After the present painstaking study of the geology of the region, and after taking into account such evidence from fossil remains and human artifacts as has been adduced, Williams is forced to the conclusion that the footprints are not less than 2000 and probably not more than 5000 years old.

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Theory of Functions of a Complex Variable. vol. I. C. Carathéodory. Trans. by F. Steinhardt. Chelsea Publ., New York, 1954. xii + 301 pp. Illus. $4.95.

The past few years have witnessed a good deal of activity in the translation of mathematical books and monographs into English. The list of outstanding books in the theory of functions of a complex variable available in English has been increased this last year by the monograph of Saks and Zygmund and now by the first volume of the *Theory of Functions*, by Carathéodory. It was with considerable excitement that the news of the original appearance of Carathéodory's *Funktionentheorie* was greeted by the mathematical public in 1950. The theory of analytic functions had been an ever-recurring theme in the research of Carathéodory. His contributions were many and significant. His monographs that had appeared hitherto (*Real Variable Theory, Calculus of Variations, Conformal Mapping*) were all of striking originality. The *Funktionentheorie*, from the time of its appearance, has had a warm reception, and its importance certainly justifies the pride that Carathéodory himself felt in his accomplishment.

The translation of this work by F. Steinhardt now renders it available to a large scientific public. In its present form it should be useful as a textbook in a course in the theory of functions of a complex variable and as a reference work in a scientific library. The first volume is elementary in scope and, of course, looks forward to the more sophisticated second volume.

The author has frankly omitted certain topics in the interest of not expanding the textbook unduly. From one point of view, the most serious omission is a systematic account of the theory of analytic continuation (however, the monodromy theorem is treated). Although the lacuna can be made up by reference to the masterful account of Saks and Zygmund, it would have been of great interest to see a treatment of this theme by Carathéodory. On the other hand, the treatment of the geometry of circles (unlike that of most books on the theory of functions of a complex variable) is extremely extensive. The justification for this elaborate treatment lies both in its pedagogic utility as an introduction to the theory of functions of a complex variable and in its value as an instrument of investigation. Other special features worthy of note are the systematic use of spherical distance (Ostrowski), the theory of normal families, and the early introduction of the Poisson integral.

An idea of the scope of the book may be had from the following summary of its contents.

Part one: "Complex numbers from the algebraic point of view"; "Geometry of complex numbers"; "Euclidean, spherical, and non-Euclidean geometry." Part two: "Convergent sequences of numbers and continuous complex functions"; "Curves and regions"; "Contour integration." Part three: "Foundations of the theory"; "The maximum-modulus principle"; "The Poisson integral and harmonic functions"; "Meromorphic functions." Part four: "Continuous convergence"; "Normal families of meromorphic functions"; "Power series"; "Partial fraction decomposition and the calculus of residues." Part five: "The exponential and trigonometric functions"; "The logarithm and the general power function"; "The Bernoulli numbers and the gamma function."

MAURICE HEINS
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Wave Motion and Vibration Theory. Proc. of Symposia in Applied Mathematics of the American Mathematical Society, vol. V. Albert E. Heins, Ed. McGraw-Hill, New York–London, 1954. v + 169 pp. Illus. $7.

This book contains a collection of 15 addresses on wave motion and vibration theory delivered at the fifth symposium on Applied Mathematics of the American Mathematical Society, held at Carnegie Institute of Technology, 16–17 June 1952. It reports the mathematical methods and the latest advances in many diverse fields of wave motion and vibration theory. These 15 papers can be grouped into approximately four broad categories:

Stability of fluid motions. C. C. Lin, "Hydrodynamic stability." A critical discussion of the linearized theory of stability of laminar parallel or nearly parallel flow is given. Many controversial points on this linearized theory are clarified. S. Chandrasekhar, "Examples of the instability of fluid motion in the presence of a magnetic field." The difference of effects of magnetic field on the thermal instability of a horizontal layer heated below and the rotational instability of viscous flow between rotating cylinders is discussed. Without magnetic fields, these two problems of instability are quite similar.

Hydrodynamic waves. P. R. Garabedian, "On free-surface flows." Researches on axially symmetric cavitational flow are reviewed. W. Bleakney, "Review of significant observations on the Mach reflection of shock waves." N. W. McLachlan, "On a nonlinear differential equation in hydraulics." The nonlinear differential equation that oc-

curs in connection with a hydroelectric power system is studied by the method of slowly varying amplitude and phase.

Diffraction and scattering problems. H. Levine, "Acoustic radiation pressure on a circular disk." W. Magnus, "Infinite matrices associated with a diffraction problem" (abstract only). A. E. Heins and H. Feshbach, "On the coupling of two half-planes." The authors are concerned with the effect of a plane wave incident upon two infinite half-planes of different acoustical materials joined along a straight line. G. F. Carrier and W. H. Munk, "On the diffusion of tides into permeable rock." The problem of water-level fluctuations in the irrigation wells is formulated mathematically by assuming the observed groundwater fluctuations to represent a diffusive transmission of the tidal disturbances through the porous volcanic structure. J. J. Stoker, "Some remarks on radiation conditions." The difficulty on the uniqueness of steady-state solution in unbounded domains may be avoided by formulating the problem as an appropriate initial value problem and then finding the solution of the steady state by limiting process in allowing time to tend to infinity. E. W. Montroll and J. M. Greenberg, "On the theory of scattering of plane waves by soft obstacles." An obstacle is considered to be soft if the wavelength of the wave inside the scatter does not differ much from that of the incident wave in the absence of the scatterer. Progress on this problem is reported.

Vibration theory. E. H. Lee, "Wave propagation in helical compression springs." A. Weinstein, "On the wave equation and the equation of Euler-Poisson." A general discussion of results on a class of hyperbolic partial differential equations which includes the classical wave equation as a special case is given. S. Lefschetz, "On the Lienard differential equation." R. J. Duffin and A. Schild, "The effect of small constraints on natural vibrations."

S. I. Pai

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Fatigue of Metals. ed. 3 of *La Fatigue des Metaux.* R. Cazaud. Trans. by A. J. Fenner. Philosophical Library, New York, 1953. 334 pp. Illus. + plates. $12.50.

This book is essentially an English translation of the author's 1948 edition of *La Fatigue des Metaux.* It discusses the characteristics of fatigue failures, theories of the mechanisms of fatigue in metals, fatigue testing machines, influence of various factors such as size, speed of test, overstress, understress, residual stress, notches, sharp shoulders, surface conditions, and corrosion. It includes a chapter on fatigue strength of structural joints and another on improving the fatigue strength of machine components.

The description of fatigue-testing machines is predominantly concerned with European practice, as would be expected. The few references to American testing machines are not representative of recent practice and do not reflect the fine work done in this field. The discussions of the effects of various factors are an interesting review and should serve as a valuable summary for engineers in general. The chapters on fatigue strength of structural joints and on improvement of fatigue strength of machine components should be of great value to designers in pointing up the practical application of the accumulated knowledge of fatigue of metals.

The book is well written and authoritative. However, it is not as modern as the date of publication (1953) would indicate. Practically all the data discussed were developed prior to 1948. Nevertheless, it is a valuable book for the practicing engineer to have on his bookshelf, for it will serve well as a ready reference on the subject.

R. R. Moore

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Statistical Analysis in Chemistry and the Chemical Industry. Carl A. Bennett and Norman L. Franklin. Wiley, New York; Chapman & Hall, London, 1954. xvi + 724 pp. Illus. $8.

Owing to the rapidly accelerating interest that has developed since 1947 in the use of modern statistical methods in the field of chemistry, the Committee on Applied Mathematical Statistics of the National Research Council and the Mathematics Branch of the Office of Naval Research have sponsored the preparation of this comprehensive book on applied mathematical statistics, with illustrative material from chemistry and the chemical industry. The authors were carefully chosen; one is a mathematical statistician with experience in chemistry, and the other is a chemist with knowledge of mathematical statistics. The sponsors and authors had the advice and cooperation of a host of statisticians and chemists of outstanding professional ability.

This remarkable planning and fine cooperation have resulted in a work of broad scope, as is indicated by its 11 chapter headings: "Introduction," "Descriptive statistics," "Probability and samples," "Mathematical machinery," "Statistical inference," "Relationship between variables," "Analysis of variance," "Design of experiments," "Analysis of counted data," "Control charts," and "Some tests of randomness."

The mathematics used is not beyond the ability of an engineering or chemistry graduate, thus placing the level between that of the standard textbooks of mathematical statistics and that of books dealing mainly with applications of statistical methods. The more theoretical topics are relegated to appendixes at the ends of several chapters. Many statistical techniques are presented and abundantly illustrated with appropriate examples from chemistry. Numerous tables make possible the numerical calculations involved in application of these techniques. However, there are no unsolved examples on which the student can test his knowledge.

Statistical Analysis can be studied with profit by physical scientists and engineers with some knowledge of statistics and by students of mathematical statistics interested in applications. However, it is doubtful whether the on-the-job chemist without formal

training in mathematical statistics can work his way through this treatise without outside assistance. For this reason it would have been helpful if the authors had indicated a selection of topics suitable for a first reading.

I heartily recommend this book to those with serious interest in the applications of statistics. However, there are several features open to criticism: (i) The authors' substitution of the symbol "ave (x)" for the universally accepted symbol "$E(x)$" is annoying to the mathematical statistician and is likely to be confused with the common use of the word *average*. (ii) Seventeen useful tables are distributed throughout Chapters 5, 6, 9, and 11 without being properly referenced, and consequently are lost to the occasional user of the book. (iii) The authors repeatedly use significance levels of the F and χ^2 distributions that are not included in their tables and fail to inform the reader of their sources. (iv) The list of references should be alphabetized. (v) The most serious criticism is the occurrence of numerous typographical errors in formulas and in numerical calculations, which tend to destroy the reader's confidence in the authors.

I feel that the afore-mentioned criticisms are sufficient justification for a revision of the book at the earliest possible date. With proper editing *Statistical Analysis* could be one of the most useful reference books on applied statistics.

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Physical Geology. L. Don Leet and Sheldon Judson. Prentice–Hall, New York, 1954. ix + 466 pp. Illus. $6.75.

A generation ago geology, as presented in textbooks, was largely a descriptive science, comparatively independent of other subjects. As knowledge has increased, so has dependence on related disciplines, and precise quantitative measurements have supplemented descriptive analyses. Elementary textbooks, however, have been slow to incorporate the advances in research and industry, although recently some have shown increasing awareness of the interrelationships of geology and other sciences. *Physical Geology* reveals in an outstanding manner the contributions to geology of recent research and of disciplines such as mathematics, chemistry, physics, and astronomy, without assuming background knowledge in these fields.

This book begins with a brief description of the scope of physical geology; moves on to a short discussion of atomic chemistry and physics, explaining such topics as mass, energy, atomic particles, isotopes, ionic radii, and ionic bonds; covers carefully and thoroughly in succeeding chapters the usual topics of an elementary textbook; and ends with a chapter on the earth's age and another on mineral deposits and fossil fuels.

Written in a concise narrative style, with more than 350 pictures and drawings, this should serve as a splendid beginning textbook. All chapters merit praise, but the one on earthquakes is perhaps most outstanding, reflecting the special interests of the senior author. Up-to-date geologic information abounds, and where conclusions are controversial, the different viewpoints are presented. *Physical Geology* is an introductory textbook that retains the best from older works and moves boldly to integrate into geology that which is useful and relevant from other sciences. May the trend continue!

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Beyond the Germ Theory. The roles of deprivation and stress in health and disease. Iago Galdston, Ed. Health Education Council, New York, 1954. viii + 182 pp. Illus. $4.

This book contains 11 chapters by nine authors and a foreword by Howard Craig, director of the New York Academy of Medicine. Iago Galdston contributed the first chapter, which gives the book its name. All the papers discuss a general theme, the influence of factors other than germs in causing disease. These factors are deprivation, stress, nutrition, and the emotions.

Part I deals with "The dynamics of deprivation and stress"; part II with "Nutritional deprivation and stress"; part III with "Psychological deprivation and stress"; and part IV with "Social stress and deprivation."

In view of the increasing emphasis on psychosomatic medicine, this book is timely and may be read with benefit by most medical men, dietitians, and social workers. Unfortunately, the chapters vary considerably in interest and readability, and many contain a great deal of excess verbiage. A notable exception is the one by Lawrence Hinkle, Jr., on "Normal stress in normal experience." Its clarity and excellent organization make it delightful reading. Most of the other chapters could have been considerably improved by careful editing.

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The World of Learning **1954.** Europa Publ., London, 1954. xii + 1030 pp. $17.50.

This 1954 edition of a well-known reference book that lists the principal international scientific and cultural organizations and, in alphabetical order according to countries, detailed information about such institutions as research institutes, learned societies, colleges and technical institutes, museums and art galleries, academies, and libraries and archives. Included are the names of key personnel in each institution listed, the foundation year of the various institutions, and the titles of publications issued by them. For easy reference, there is an index of institutions.—D. R.

New Books

Tropical Soils. A critical study of soil genesis as related to climate, rock and vegetation. E. C. J. Mohr and F. A. Van Baren. N. V. Uitgeverij W. Van Hoeve, The Hague–Bandung; Interscience, London–New York, 1954. 498 pp. $8.

Release of Latent Business. A depression-proof economy; the abolition of unemployment. Emil E. Sundquist. Business Release, Rockwood, Mich., 1954. 160 pp. $2.50.

Organic Syntheses. An annual publication of satisfactory methods for the preparation of organic chemicals. vol. 34. William S. Johnson, Ed. Wiley, New York; Chapman & Hall, London, 1954. 121 pp. $3.50.

Modern Science and God. P. J. McLaughlin. Philosophical Library, New York, ed. 2, 1954. 89 pp. $2.75.

Proceedings of the First World Conference on Medical Education, London, 1953. Held under the auspices of the World Medical Association. Hugh Clegg, Ed. Oxford Univ. Press, London–New York, 1954. 804 pp. $16.

The Psychological Variables in Human Cancer. Symposium presented at VA Hospital, Long Beach, Calif., 23 Oct. 1953. Joseph A. Gengerelli and Frank J. Kirkner, Eds. Univ. of California Press, Berkeley–Los Angeles, 1954. 135 pp. $3.

Sex and Morality. Abram Kardiner. Bobbs-Merrill, New York, 1954. 266 pp. $3.

Advanced Organic Chemistry. E. Earl Royals. Prentice-Hall, New York, 1954. 948 pp. $12.

The Third Revolution. A study of psychiatry and religion. Karl Stern. Harcourt, Brace, New York 17, 1954. 306 pp. $4.

Fluoridation as a Public Health Measure. James H. Shaw, Ed. AAAS, Washington 5, 1954. 232 pp. $4.50; AAAS members, $4.

Textbook of Physics. R. Kronig, Ed. In collaboration with J. de Boer, H. C. Burger, P. H. Van Cittert, C. J. Gorter, A. C. S. Van Heel, P. Van der Leeden, and G. J. Sizoo. Interscience, New York; Pergamon, London, 1954. 855 pp. $10.

Chemical Specificity in Biological Interactions. Harvard Mem. No. 3, Frank R. N. Gurd, Ed. Academic Press, New York, 1954. 234 pp. $6.

Life on Other Worlds. Harold Spencer Jones. English Universities Press, London, rev. ed. 2, 1954 (Distrib. by Macmillan, New York 11). 259 pp. $3.

The Language of Taxonomy. An application of symbolic logic to the study of classificatory systems. John R. Gregg. Columbia Univ. Press, New York 27, 1954. 70 pp. $2.50.

Elements of Ecology. George L. Clarke. Wiley, New York; Chapman & Hall, London, 1954. 534 pp. $7.50.

Pharmacology in Medicine. A collaborative textbook. Victor A. Drill, Ed. McGraw-Hill, New York–London, 1954. 87 chapters. $19.50.

Hugh Roy Cullen: A Story of American Opportunity. Ed Kilman and Theon Wright. Prentice-Hall, New York, 1954. 376 pp. $4.

Science Funbook. Gerald M. Straight. Hart, New York, 1954 (For ages 10–15). 159 pp. Paper, $1.25.

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Technical Papers

Critical Evaluation of Feulgen Microspectrophotometry for Estimating Amount of DNA in Cell Nuclei

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In recent years, microspectrophotometry of the Feulgen stain (*1*) has been extensively used as a method for determining amounts of desoxyribosenucleic acid (DNA) in individual cell nuclei (*2–4*).

In spite of certain obvious advantages of this procedure which permits the DNA analysis of a single nucleus *in situ* directly under the microscope and its applicability to the study of the significance of DNA values in a single cell or cell type, the microspectrophotometric method of the Feulgen stain is by no means generally accepted. Based mainly on theoretical considerations of the physical and optical factors involved in the method, the microspectrophotometric method has been repeatedly criticized (*5*) and its validity seriously questioned (*6*).

While the study of such potential sources of error is fully recognized as one of the necessary criterions for the evaluation of Feulgen microscpectrophotometry, we feel that some clarification of the problem might also be derived from a survey of the results obtained by microspectrophotometric analysis and by a comparison of such results with those obtained by other methods.

In this paper, an attempt is made to evaluate the validity of Feulgen microspectrophotometry by using, as a baseline, DNA data of 15,000 nuclei as determined by this method in this laboratory (*7*). Such an approach seems justified because of the considerable number of determinations done under strictly standardized and controlled conditions on a variety of tissues. Furthermore, whenever possible, the Feulgen data were checked by other independent methods. Ultraviolet microspectrophotometry, chromosomal studies, as well as DNA determinations by biochemical analysis, were carried out simultaneously on the same material.

The data presented in Table 1 may be considered mainly from two points of view which seem pertinent in examining the validity of a method: (i) How do the DNA results obtained by microspectrophotometry of the Feulgen stain compare with DNA results by other analytic methods? (ii) How sensitive is this method? In other words, what is the degree of accuracy with which amounts of DNA can be safely determined?

Comparing first the DNA data by Feulgen microspectrophotometry with the results of the biochemical analysis, it can be seen that there is a striking agreement of both methods, giving 1 DNA, 2 DNA, 4 DNA for bull sperm, normal somatic beef, and rodent tumor nuclei, respectively.

It can also be seen that if a tissue, such as rat liver, which contains nuclei with different amounts of DNA (2 DNA, 4 DNA, 8 DNA), is examined, only the microspectrophotometric analysis of *individual nuclei* is capable of reflecting the individual DNA classes, whereas the biochemical analysis that is done on a mass of nuclei can of necessity give only an average value.

The second standard method that can also be used

Table 1. Comparison of the content of DNA in 15,000 individual animal nuclei by microspectrophotometry of the Feulgen stain and other analytical methods. Amounts of DNA are given in basic arbitrary units.

Type of material	Chromosomal counts	DNA by Feulgen* microspectrophotometry	DNA by ultraviolet† microspectrophotometry	DNA by biochemical analysis
Human sperm	1n, haploid	1 DNA		
Bull sperum		1 DNA	1 DNA	1 DNA*†
Insect spermatid (Arvelius)		1 DNA		
Beef liver, beef kidney	2n, diploid	2 DNA	2 DNA	2 DNA*†
Rodents: kidney, spleen, lymphoma		2 DNA	2 DNA	2 DNA†
Rodents: Ehrlich ascites tumor	4n, tetraploid	4 DNA	4 DNA	4 DNA†
Rat liver	2n, diploid	2 DNA	2 DNA	Average value
	4n, tetraploid	4 DNA	4 DNA	of all
	8n, octoploid	8 DNA	8 DNA	DNA classes*†
Hamster liver		2 DNA		
		4 DNA		
		8 DNA		
Human liver	2n, diploid	2 DNA		
	4n, tetraploid	4 DNA		
	8n, octoploid	8 DNA		

* Studies done at the Institute of Pathology, Western Reserve University, Cleveland, Ohio.
† Studies done at the Karolinska Institute, Stockholm, Sweden.

as a tool for the critical examination of Feulgen microspectrophotometry is the counting of chromosomes. It is evident that there is a good accordance between the DNA results of Feulgen microspectrophotometry and chromosome numbers, a comparison that is of special significance in tissues showing multiple DNA values.

The third method used for comparison concerns DNA determinations by *ultraviolet* microspectrophotometry. Although it may be argued that another microspectrophotometric method is not too suitable for comparison, nevertheless, the different principles of the two methods and accordance of the ultraviolet data with the Feulgen data are of sufficient interest to justify its inclusion in Table 1.

Coming now to the second point—namely, the sensitivity and accuracy of the microspectrophotometric DNA determinations—the excellent agreement of the *multiple* DNA values obtained by Feulgen microspectrophotometry with chromosome numbers, as well as with biochemical analysis, illustrates the order of magnitude with which the method can be safely used. Even if the actual DNA values obtained by microspectrophotometry of the Feulgen stain may sometimes show variations up to 15 percent from the theoretical ratios of 1:2:4:8 DNA, such a difference would hardly be capable of obscuring the multiplicity of the DNA values.

On the other hand, the question of the significance of *intermediate* DNA values occurring in nuclei cannot be so readily answered. Although there does not seem to be any doubt about the constant occurrence of such intermediated DNA values in nuclei of proliferating tissues (*3, 8*) it is felt that much more work and probably more exact methods are needed to interpret the degree of accuracy of the intermediate values.

On the basis of the data presented in Table 1, it seems justifiable to say that microspectrophotometry of Feulgen stain can be utilized as a reliable tool for the comparison of relative amounts of DNA in nuclei of different cells, provided that the differences to be detected are sufficiently large.

In support of the validity of the method, it may be added that microspectrophotometry of Feulgen stain also permits an excellent reproducibility of the DNA results, if preparation of nuclei and measurements are done under carefully standardized and controlled conditions. In this laboratory, a group of 12 trained workers, using four different microspectrophotometric setups within a period of more than 4 years, obtained nearly identical DNA results in the same tissues, the largest variation ever encountered being 10 percent. Furthermore, results from other laboratories are essentially in accordance with the data presented in Table 1 (*2–4*).

Taking into consideration the reproducibility of the DNA data obtained by Feulgen microspectrophotometry, their good correlation with chromosomal counts, with ultraviolet microspectrophotometry, and with the biochemical analysis, one can hardly escape the conclusion that the method has its merits and can be used safely for DNA determination at this level of investigation. This, of course, does not exclude the necessity of cautious interpretation, of checking the DNA data by other methods, and of the possible interference of other factors (*5*), if the method is used for the detection of smaller differences in DNA content.

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Hexokinase Reversibility Measured by an Exchange Reaction Using C^{14}-Labeled Glucose

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In the hexokinase reaction, a phosphate group is transferred from adenosine triphosphate (ATP) to glucose to form glucose-6-phosphate:

$$\text{ATP} + \text{glucose} \rightleftharpoons \text{glucose-6-phosphate} + \text{ADP}.$$

The reaction from left to right is associated with a large loss of free energy, and hence equilibrium is far to the right. Net synthesis in the reverse direction has not been demonstrated. In the present study (*1*) evidence of reversibility was obtained by observing an exchange between glucose and glucose-6-phosphate with the aid of C^{14}-labeled glucose. The exchange reaction was found to require catalytic amounts of either ATP or ADP.

The enzyme used in this study was purified from yeast using the method of Berger *et al.* (*2*), the preparation, essentially fraction V, contained 800 units per milligram of protein and, hence, was considered 26-percent pure. Phosphohexose isomerase was present as a significant impurity. During the prolonged reaction times used in this study, this latter enzyme functioned to bring the glucose-6-phosphate $\rightleftharpoons$ fructose-6-phosphate reaction to its equilibrium and, thus, to convert approximately one-third of the glucose phosphate to its fructose isomer. Phosphoglucomutase was also present as a contaminating enzyme. Phosphatase was not detected. The hexokinase proved durable, re-

taining most of its activity during 16-hr incubation periods at 30°C.

Glucose-6-phosphate was measured using the Zwischenferment system (*3*). The Zwischenferment was obtained from *Leuconostoc mesenteroides* (*4, 5*). Fructose-6-phosphate was determined using the resorcinol method of Roe (*6*). Radioactivity was assayed at "infinite thinness" by drying 0.2 ml aliquots on planchets and counting with a standard end-window Geiger tube or, when necessary, with a continuous-flow gas counter. In the four experiments in which the specific activity of the hexose phosphate was the lowest, the counts per minute were 25 above background with a standard error of the counting rate of 10 percent. In all other studies the standard error was less than 5 percent. The glucose was separated from the hexose phosphates chromatographically using a small Dowex-1 formate column (5 mm high, 8 mm in diameter). The glucose was confined to the effluent. The glucose-6-phosphate and the fructose-6-phosphate were eluted, without significant separation, with 10 to 20 ml of buffer (sodium formate 0.05*M* and hydrochloric acid 0.002*M*, *p*H 5.0). ATP was assayed using hexokinase. ADP was measured by coupling hexokinase with myokinase.

The exchange reaction was followed by determining the specific activity of hexose phosphate (glucose-6-phosphate and fructose-6-phosphate) and comparing it with the theoretical activity of complete exchange. The latter value was obtained by dividing the total counts recovered from the column by the total micromoles of glucose and of hexose phosphate recovered. The specific activity of the two hexose phosphates was assumed to be equal. In four experiments, each with a 16-hr reaction period and in which no ADP or ATP was added, no radioactivity was detected in the eluates that contained the hexose phosphates. The results shown in Fig. 1 indicate faster exchange rates with increasing concentrations of ADP or ATP. The exchange appeared to be as well implemented by ADP as by ATP. In the ATP experiments the results were corrected quantitatively for the glucose phosphorylated directly by the "forward" reaction.

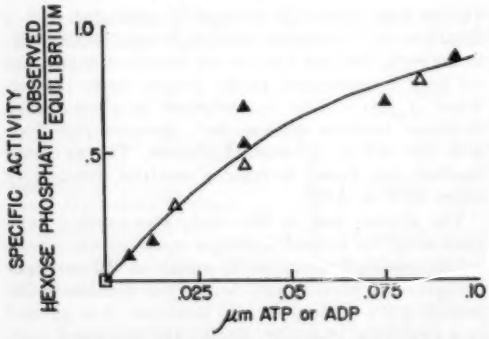

Fig. 1. Hexokinase exchange reaction. The reaction mixture consisted of 250 units of hexokinase, 2 μM of glucose, 2 μM of glucose-6-phosphate, and 0.05 μc (5000 counts/min) of C^{14}-labeled glucose (0.1 mg) in 0.01*M* $MgCl_2$ and 0.03*M* "Tris" buffer (*p*H 7.6). The total volume was 0.3 ml. The mixture was incubated for 16 hr at 30°C. □ represents four experiments, no added ATP or ADP; ▲, ATP; △, ADP.

In preliminary experiments, in which the amount of ADP added was increased to 5 μM, 25- to 50-fold increases in the exchange rate have been demonstrated. The exchange reaction has been observed with two other preparations of yeast hexokinase; the first was prepared using an extensive modification of the Berger procedure and the second was given to us by C. R. Park, who used a different purification method.

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* U.S. Public Health Service postdoctorate fellow.
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3 September 1954.

Effects of Light Intensity and Nitrogen Growth Source on Hydrogen Metabolism in *Rhodospirillum rubrum*

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The photosynthetic nitrogen-fixing bacterium *Rhodospirillum rubrum* produces molecular hydrogen photochemically during growth in media containing certain amino acids but does not do so when an ammonium salt is the nitrogen source (*1*). Resting cells derived from the former type of medium similarly catalyze light-dependent evolution of H_2 in the presence of various organic compounds (photo-evolution), and it has been shown that formation of this product by such cells is inhibited by addition of N_2 or ammonium salts (*1*). These observations indicate a close relationship between nitrogen metabolism and H_2 formation. The latter process in *R. rubrum* and physiologically similar organisms may be regarded as a manifestation of photochemical "reducing power." It is presumed that the terminal catalyst required for H_2 formation is the enzyme hydrogenase, which is ordinarily assayed by manometric measurement of H_2 utilization in the presence of a suitable electron acceptor (for example, ferricyanide in the present experiments) (*2*). Several types of evidence also suggest an important role for hydrogenase in the N_2 fixation process in aerobic nonphotosynthetic agents such as *Azotobacter*. In this connection, it is generally considered significant that cells of *Azotobacter* grown on N_2 usually show considerably higher hydrogenase activity than cells grown with ammonium salts as the nitrogen source (*3*).

As a first approach to closer study of the function

of hydrogenase in nitrogen metabolism in *R. rubrum* (strain SI), we have investigated (*4*) the relative activities of hydrogenase and the photoevolution system in resting cells obtained from glutamate plus malate and NH_4Cl plus malate media. The former medium was prepared as described in an earlier publication (ref. *5*, G3X medium), with the exception that the yeast extract concentration was reduced from 600 to 400 mg/lit; the NH_4Cl plus malate medium was identical in all respects, except that 1 g of NH_4Cl per liter was substituted for the glutamate. In all instances the experimental cultures were sown with a 1-percent inoculum from a 24-hr culture grown in a complex nitrogen-rich medium (see G5 medium, ref. *5*). The bottle cultures (125 ml) were maintained at 30°C either 18.5 or 33 in. from a 150-w General Electric reflector flood lamp and were consequently exposed to average intensities of approximately 400 or 130 ft-ca, respectively.

Typical data illustrating cell yields obtained in the two media, as well as the hydrogenase and photoevolution activities of the harvested cells, are listed in Table 1. The results of two separate experiments at each age and light intensity (during growth) are given in terms of milligrams dry weight of cells per liter (cell yield) or $QH_2(N)$—that is, microliters of H_2 evolved or utilized per hour per milligram of cell nitrogen at 30°C. There was no appreciable dilution effect on the hydrogenase or photoevolution activities over the range of cell concentrations used in the assays.

It is evident that growth in both media is greatly enhanced by increase of light intensity from 130 to 400 ft-ca. The cell yield data also suggest that glutamate nitrogen is assimilated more readily than ammonia nitrogen during the first 24 hr. In accord with the results previously noted in growing culture experiments, resting cells derived from the ammonia medium do not produce H_2 photochemically. The ability of glutamate-grown cells to catalyze photoevolution (from pyruvate) is considerably greater in organisms grown at 400 ft-ca than in those grown at the lower light intensity. In contrast with "400 ft-ca cells," organisms cultivated at 130 ft-ca produce H_2 at the rates indicated only after an appreciable induction period. The $QH_2(N)$ values for photoevolution show a definite rise with increasing cell age at both light intensities.

Although incapable of photoevolution, ammonia-grown cells contain hydrogenase and the $QH_2(N)$ of this activity is seen to increase markedly with age. A light-intensity effect, comparable to the one already discussed, has been consistently noted in 48-hr and older cells. Pyruvate is rapidly decomposed in the light by ammonia-grown cells with the liberation of CO_2 (for example, $QCO_2(N)$ of 200 observed with 72-hr cells), and it appears that failure to produce H_2 is not the result of a deficiency of hydrogenase. It also seems unlikely that lack of H_2 formation could be entirely due to utilization of metabolic hydrogen for reductive amination of pyruvate with intracellular ammonia. The present results suggest the possibility that a specific electron transport system is required in addition to the hydrogenase enzyme (as measured here) for evolution of H_2 and that the former is not produced in cells growing with ammonia as the sole source of nitrogen.

The hydrogenase activity level in cells grown on glutamate does not increase as greatly with age as is the case when ammonia is the nitrogen source, and a light-intensity effect, although frequently noted, has not been uniformly found. It is evident that the relative hydrogenase activities of the two nutritional types is greatly influenced by age and thus there is no apparent *unique* relationship between nitrogen growth source, comparing ammonia and glutamate, and capacity to activate H_2 for reduction of ferricyanide.

As is indicated by the data in Table 1, all the cell types examined thus far that were capable of photoevolution of H_2 displayed hydrogenase activity, whereas the converse does not necessarily hold. Since the requirements for *rapid* growth (24 to 72 hr) of

Table 1. Hydrogen metabolism and cell yields of *R. rubrum* grown under different conditions.

Age (hr)	Activity	Cells from glutamate medium				Cells from ammonia medium			
		130 ft-ca		400 ft-ca		130 ft-ca		400 ft-ca	
24	Hydrogenase*	136	200	127	146	48	98	36	
	Photoevolution†	0	36	63	100	0	0	0	
	Cell yield‡	220	220	440	490	90	120	120	
36	Hydrogenase	155	146	209	318	77	32	74	24
	Photoevolution	56	57	182	200	0	0	0	0
	Cell yield	490	480	890	990	420	370	920	920
69	Hydrogenase	307	300	364	307	492	492	764	800
	Photoevolution	138	100	264	209	0	0	0	0
	Cell yield	940	800	1350	1400	810	1070	1280	1460

* *Hydrogenase assay*: Results expressed as microliters of H_2 utilized per hour per milligram of cell nitrogen at 30°C. Water-washed cells were suspended in 0.125*M* phosphate buffer pH 6.8; final fluid volume, 2 ml. At zero time, 166 μM of $K_3Fe(CN)_6$ was added. KOH present in center well of the Warburg vessel. Gas phase, hydrogen. Dark.

† *Photoevolution assay*: Results expressed as microliters of H_2 produced per hour per milligram of cell nitrogen at 30°C. Water-washed cells were suspended in 0.05*M* phosphate buffer pH 6.7; final fluid volume, 2 ml. At zero time, 50 μM of sodium pyruvate was added and illumination begun (approx. 1000 ft-ca). KOH present in center well. Gas phase, helium.

‡ Milligrams dry weight per liter.

R. rubrum with N_2 as the sole or primary nitrogen source are still unknown, comparable experiments with such cells have not yet been possible. These nutritional requirements are now under investigation.

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23 August 1954.

On the Anti-inflammatory Mechanism of Hydrocortisone (Compound F)

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My earlier studies (1940, 1942) have indicated that adrenocortical extract or cortisone suppresses the increased permeability of small blood vessels caused by an alkaline exudate or its contained leukotaxine. Subsequently, it was shown that cellular activity, as gaged by the incidence of cell division, was considerably reduced in the eggs of the sea urchin, *Arbacia punctulata* by the presence in sea water of corticosteroids (*1–6*). Severely injured cells, such as those encountered in acute inflammation, liberate, as a result of their activity, numerous chemical factors capable of reasonably explaining the various manifestations of inflammation (*7*). These factors include, among others, leukotaxine and the leukocytosis-promoting factor (LPF). Leukotaxine explains the initial increased small blood vessel permeability and the migration of polymorphonuclear leukocytes into an inflamed area (*7, 8*). The LPF induces a discharge of leukocytes from the bone marrow and in part explains the mechanism of leukocytosis often accompanying an acute inflammation (*7*). Observations were undertaken (*9*) to determine whether the presence of compound F in an inflamed area would suppress the activity of injured cells, so that they no longer would be able to produce adequate amounts of active leukotaxine or of the LPF (*10*).

Acute inflammation was induced in dogs by the intrapleural injection under pentobarbital anesthesia of 1.5 ml of turpentine. The experimental animals were then injected at the same site with a suspension in saline of 10 to 20 mg hydrocortisone (compound F, free alcohol) (*11*), repeated at daily intervals for 3 to 4 days. The control dogs, following the intrapleural injection of turpentine, received daily injections of saline into the inflamed area. The increased permeability of the small blood vessels was determined, as was previously described, by the extent of accumulation of intravenously injected trypan blue into the treated cutaneous areas on the abdomen of rabbits (*1–4, 6*).

Leukotaxine was extracted, as is described elsewhere, from a given sample of exudate withdrawn from the chest cavity of experimental and control dogs (*12, 13*). Following repeated injections of hydrocortisone (compound F) into the inflamed area, the activity of leukotaxine in regard to its capacity of increasing small vessel permeability was considerably reduced (Table 1, Fig. 1). The outward migration of leukocytes

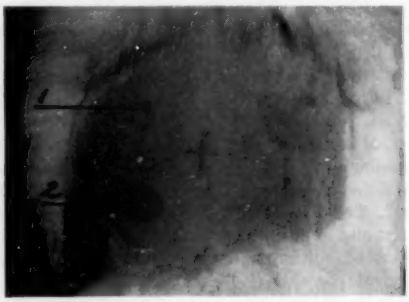

Fig. 1. Inability of leukotaxine derived from compound F-treated exudate to induce increased permeability of small blood vessels. Rabbit 21–19: *Area 1*, 0.4 ml of leukotaxine extracted from exudate of dog 254-T following two successive daily injections of compound F into inflamed area. Total of about 42 mg of hydrocortisone in 6 ml of saline injected into inflamed pleural cavity of the dog from which leukotaxine had been extracted from a given quantity of exudative material. *Area 2*, 0.4 ml of leukotaxine extracted from exudate of dog 255-T following two successive injections of a total of 6 ml of saline into inflamed area. Leukotaxine extracted from an identical quantity of exudative material as in the case of dog 254-T. At end of experiment 6 ml of 1-percent trypan blue in saline was injected intravenously. The injections of areas 1 and 2 were made in the dermis of the abdomen.

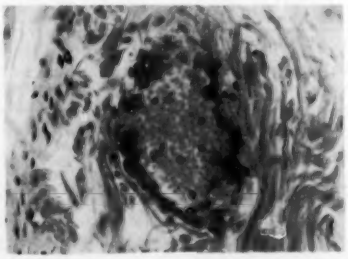

Fig. 2. Effect of leukotaxine in inducing margination of polymorphonuclear leukocytes in skin of rabbit 21–22. Taken about 1 hr after intracutaneous injection of leukotaxine extracted in turn from a sample of canine exudate. The exudate was derived from the pleural cavity of a dog previously injected with turpentine into that region. The animal had received two successive daily injections of saline, each 3 ml. The section is that of a small blood vessel, possibly a venule. (×200)

Table 1. Inhibition of increased capillary permeability caused by leukotaxine upon repeated injections of compound F into an inflamed area. Commercial hydrocortisone was used with rabbits 21–21 and 21–22; compound F (free alcohol) was used in all other experiments.

Rabbit	Compound F injection		Total vol. of saline inj. into inflamed area of control dog (ml)	Accumulation of trypan blue in cutaneous areas treated with	
	No. of inj. into original area of inflammation	Total amt. inj. into inflamed area (mg)		Leukotaxine from compd. F-treated exudate	Leukotaxine from control saline-treated exudate
21–27	1	24	4	3+	2+ to 3+
21–18	1	21.9	3	Trace	+
21–31	1	11		2+	
	3	37.6	8	Trace	2+
21–19	2	42	6	0	3+
21–21	2	40	6	0	2+ to 3+
	2	40	6	Trace to +	
21–22	2	40	6	Trace	+

Table 2. Summary of observations on the effect of the LPF of exudates following repeated injections of compound F (free alcohol) into an inflamed area. Commercial hydrocortisone was used with dogs 249-T and 264-T; compound F was used in all other experiments.

Dog	Control dog		Experimental dog		
	Amt. of LPF inj. (ml)	Rise in white blood cell count (%)	Total amt. of compd. F used (mg)	Amt. of LPF inj. (ml)	Rise in white blood cell count (%)
256-T	30	158.1	41.9	30	89.0
8-D	±18	77.6	20.0	20	51.4
171-T	20	62.2	20.0	20	30.6
267-T	±23	78.2	24.0	25	31.8
282-T	±23	88.1	11.0	24	34.3
249-T			40.0	21	55.7
264-T			40.0	20	48.0
χ			34.2	30	50.3
Avg.		92.8			48.9

as induced by leukotaxine is also conspicuously diminished following repeated injections of compound F into the inflamed area (Figs. 2 and 3). Diapedesis of leukocytes occurs through both capillaries and venules; and this, in contrast to the findings in controls (Fig. 2), is relatively absent with the use of leukotaxine extracted from experimental exudates (Fig. 3).

The LPF was extracted, as is described elsewhere (7), from a given sample of alkaline exudative material obtained from control and experimental dogs. The results are summarized in Table 2. It is clear that the

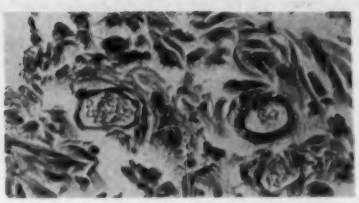

Fig. 3. Small blood vessels in skin of rabbit injected with leukotaxine extracted from an exudate of a dog that had previously received two successive injections of compound F into its inflamed pleural cavity. The small blood vessels appear to be a capillary on the left and possibly an arteriole on the right. Diapedesis of leukocytes through the capillary wall is absent. (×200 approx.)

repeated local injections of hydrocortisone (compound F) into the inflamed area yielded in the exudate an LPF, on the average about half as potent as that obtained from control samples. The course of one such experiment is illustrated in Fig. 4. The discharge of immature polymorphonuclear leukocytes (1-lobe form) is likewise inhibited by compound F administration (Table 3).

The LPF when mixed *in vitro* with compound F is not altered in its capacity to increase the number of circulating leukocytes. This was demonstrated in three separate experiments by adding 15 to 21 mg of compound F to about 50 mg of LPF and maintaining the mixture *in vitro* for 18 to 19 min prior to intravascular injection into dogs. There was no reduction in the activity of the LPF, the experimentally treated dogs inducing an average rise in the WBC of 130.1 percent as against 111.4 percent in the controls. This evidence supports the view that hydrocortisone injected directly into the inflamed area suppresses the activity of the injured cells in forming the LPF rather than

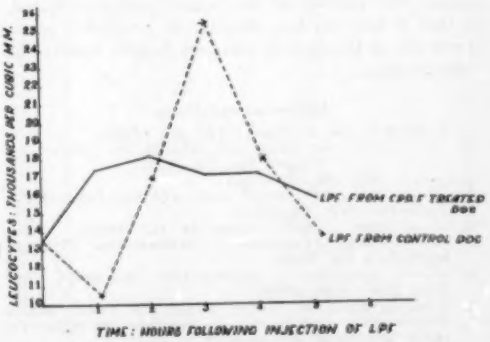

Fig. 4. Partial inactivation of the LPF of exudate by direct injections of compound F into the inflamed area of dog 282-T. The amount of LPF tested in this experiment was recovered from 8 ml of exudate derived either from a compound F-treated dog or from the control sample of exudative material. [Graph prepared by William Rogers]

Table 3. Summary of observations on the discharge of immature polymorphonuclear leukocytes (1-lobe form) following injections of LPF after repeated administration of compound F into inflamed area. The figures are averages of five observations in each control and experimental group.

	Control dog	Experimental dog
Total amount of saline or of compound F administered	5.9 ml	19.4 mg
Basal number of 1-lobe form	18.4%	22%
Highest number of 1-lobe form following injection of 15 to 20 ml of LPF	54.4%	33.6%

interacting directly with the preformed LPF at the site of inflammation.

In the case of leukotaxine, the sole observations reported here do not justify a similar inference, inasmuch as earlier studies had demonstrated that leukotaxine *per se* mixed *in vitro* with cortisone or compound F is to a large extent inactivated (*2, 12*). It is, of course, conceivable that both direct interaction with leukotaxine by the corticosteroid and suppression of formation of this substance in injured cells may occur. It is scarcely conceivable that any of the difficultly soluble corticosteroid would be carried along in the chemical extraction of leukotaxine from the exudate (*6, 12*). This likewise would hold for the extraction of the LPF where exclusively a protein "salting out" process with $(NH_4)_2SO_4$ is utilized (*7*). Furthermore, the *in vitro* observations with the LPF described here indicate that the corticosteroid has no effect on the LPF *per se*.

In conclusion, the evidence briefly reported here indicates that the anti-inflammatory mechanism of compound F can be explained as acting at a cellular level (in distinction to molecular, enzymatic, or other levels). The activity of the injured cell is impaired, so that it becomes less effective in producing some, if not all, of the specific chemical factors involved in inflammation.

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27 August 1954.

Occurrence of a Pungent Insecticidal Principle in American Coneflower Roots

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A number of insecticidal unsaturated isobutylamides have recently been isolated from natural sources (*1*). They all possess a high order of pungency. A small amount placed on the tongue causes profuse salivation and a burning, paralyzing effect on the tongue and mucous membranes. They are very closely interrelated structurally, the acid components containing an unbranched chain of 10 to 18 carbon atoms and at least two double bonds.

During an investigation of scabrin (*2*), one of the most active of these compounds, which occurs in the roots of *Heliopsis helianthoides* var. *scabra* (family Compositae), it was learned (*3*) that the roots of the American coneflower, *Echinacea angustifolia* DC., a closely related plant, are highly pungent when chewed. A search of the literature revealed that this property had previously been noted (*4*) and that an acetone extract of the roots contains a mosquito larvicide (*5*). In addition echinacoside, $C_{35}H_{46}O_{20}$, which was isolated from the methanol extract of the roots by Stoll *et al.* (*6*), possesses antibacterial properties. The American coneflower is indigenous to Kansas, Nebraska, and Missouri. The roots are used medicinally in the healing of wounds and inflammations and are available commercially.

The dried roots (*7*) were ground and extracted successively in a Soxhlet extractor with *n*-pentane, ethyl ether, chloroform, and ethanol, and the solvent-free extractives were tested separately in refined kerosene solution against adult houseflies, *Musca domestica* L., by Norman Mitlin. Only the pentane extractive, consisting of 4 percent of a highly pungent yellow oil, was toxic to these insects, showing high knockdown and fair mortality. A considerable quantity of an inactive colorless, liquid hydrocarbon, bp 85°C (0.5 mm-Hg), N_D^{25} 1.4488, was obtained from the extractive by distillation. These constants correspond to those reported by Woods (*8*) for the unidentified hydrocarbon $C_{15}H_{28}$ isolated previously from *E. angustifolia* roots. The activity was found to be concentrated in the neutral fraction, a viscous yellow oil that solidified when cooled to 5°C, after separation of the inactive mixed-acids fraction from the distillation residue. By dissolving the solid in petroleum ether (bp 60° to 80°C), cooling the solution at −78°C, filtering off the resulting amorphous solid, and recrystallizing it several times from the same solvent at −10°C, there was obtained 250 mg (0.0004 percent of the dry root) of colorless needles, mp 63° to 64°C. This material had the characteristic numbing effect on the tongue and possessed moderate insecticidal activity in tests with houseflies. The compound has been designated *echinacein*.

Attempts to identify echinacein were greatly hampered by the fact that the crystals are highly unstable, polymerizing in the air after 1 hr at room temperature and after 2 days in a nitrogen atmosphere at −10°C (a natural antioxidant is apparently present in the crude extract of the roots). The compound showed a maximum in the ultraviolet at 259 mμ, characteristic of a conjugated triethenoid structure, and analyzed fairly well for $C_{16}H_{25}NO$. Hydrogenation in ethanol solution with a platinum catalyst gave colorless needles, mp 51° to 52°C, identical with N-isobutyllauramide. Permanganate oxidation of echinacein resulted in a mixture of acids, none of which were present in sufficient amount for identification. One of these acids, volatile with steam, consisted of a few drops of a colorless, highly corrosive oil with a penetrating unpleasant odor. Accidental contact of a trace of this acid with the skin of the hand caused an immediate burning sensation and rapid blistering of the skin at the site of contact, followed by peeling of the skin after 2 days.

Echinacein appears to be the isobutylamide of a highly unsaturated 12-carbon straight-chain acid and may be identical with neoherculin, mp 63° to 65°C, isolated by Crombie (*9*) from the bark of *Zanthoxylum clava-herculis*. Further identification must await the isolation of larger quantities of pure material.

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1 September 1954.

Utilization and Intestinal Excretion of Calcium in Man

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Data on Ca^{45} metabolism in man have been reported and measurements of endogenous fecal calcium and the utilization of ingested calcium have been discussed (*1*). In this study the rate of absorption and utilization of ingested calcium, the excretion of digestive juice calcium into the gastrointestinal tract and its reabsorption were measured with the Ca^{45} technique and metabolic balances (*2*). Two patients without bone disease, B and L, maintained on low calcium diet, received a single dose of 50 μc Ca^{45} with 30 mg of calcium carrier orally. Serum, urine, and stool were analyzed for calcium and Ca^{45} (Fig. 1). Balances of calcium, phosphorus, and nitrogen were measured for four 6-day periods (Table 1).

The top graph of Fig. 1 shows the specific activities of serum and urine and the serum Ca^{45} levels of patient B in the first 24 hr. Radioactivity was first detected in blood at 15 min; a 5-min sample had no activity. The specific activities of blood and urine from the second day to the termination of the experiment are plotted on a semilogarithmic scale in Fig. 1. There is a simple exponential decline with a half-time of 8 days. The first stool collected at 2 hr contained no activity; the next specimen at 25 hr, 5.0 percent; after a 5-day period a total of 58 percent of the dose was excreted. The specific activity of these samples is not plotted, since it was considerably higher than 1 percent of the dose per 100 mg of Ca. Figure 1 shows

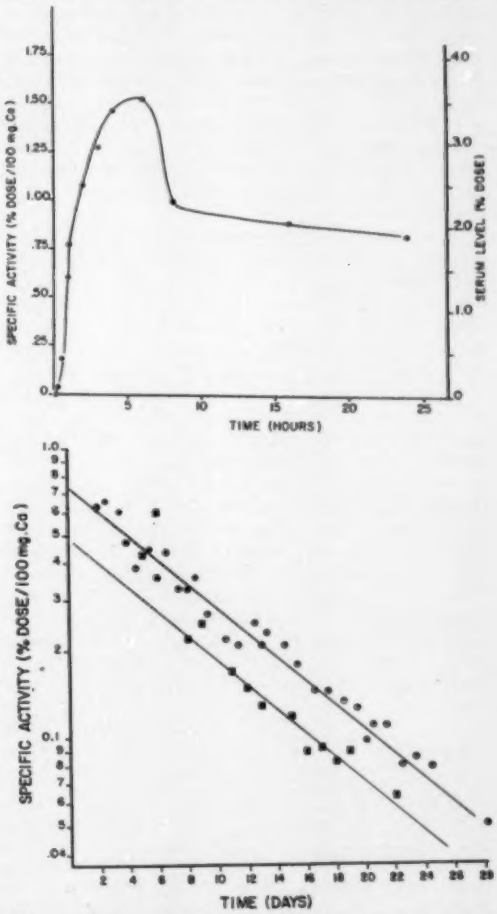

Fig. 1. Calcium and Ca^{45} content in serum, urine, and stool of two human patients. Symbols: ● plasma, ⊙ urine, ■ stool.

the specific activity of stool collected after the fifth day. After 1 wk the specific activity of the stool calcium falls exponentially on a line parallel to, and below, the blood and urine line.

Data obtained in the simultaneous study of patient L were similar to those of B. Blood taken at 15 min contained no Ca^{45}, whereas it was radioactive at 30 min, with the peak occurring at 2 hr (3.4 percent of dose). Urine collected in the first hour was radioactive; the 2- to 4-hr sample had the highest specific activity. The specific activities of plasma and urine were equal and fell exponentially with a half-time of 9 days. The specific activity of the stool was high for several days and then fell on a line parallel to, and below, the urine and serum level.

The radiocalcium content and the specific activities of serum and urine in the early phases (top graph, Fig. 1) illustrate the rapidity with which ingested calcium is absorbed, probably from the uppermost segments of the intestinal tract. The specific activities of serum and urine become rapidly equal, urines of the first and second hour, respectively, fall already on the serum curve. After this early phase, the specific activity of serum and urine decline exponentially with an 8- or 9-day half-time. Similar results were obtained in patients given Ca^{45} intravenously, which implies that the metabolic pattern is independent of the route of administration following the initial period of absorption.

In the early phase of the experiment the stool radiocalcium derives from two sources: unabsorbed ingested Ca^{45} and Ca^{45} carried into the tract with digestive juices. These juices probably become radioactive almost immediately after the dose is given and have the same specific activity as blood and urine. During the passage of the unabsorbed dose (about 1 wk) the stool has a high specific activity, whereas at the end of this time values fall on a line parallel to, and below, the urine-blood line (Fig. 1). At this time the only source of stool Ca^{45} is digestive juice calcium, which enters the tract with the specific activity of plasma calcium but is diluted by nonradioactive unabsorbed food calcium. Ratio of the specific activities of stool: plasma or urine represents the fraction of stool calcium that is endogenous, that is, intestinal juice calcium (*3*). The endogenous calcium calculated in this manner averaged 91 mg/day for B, 117 mg/day for L. The remainder of 60 mg and 45 mg fecal calcium per day, respectively, is unabsorbed food calcium. Subtracting these values from the intake (Table 1), the utilization of ingested calcium was calculated to be 44 percent for B and 67 percent for L.

The utilization can also be determined from the unabsorbed Ca^{45} in the stool. The total excretion of Ca^{45} in stool for B during the period the unabsorbed dose was passed (first week) was 60 percent. During this time, however, endogenous fecal Ca^{45} had also been excreted, for which a correction must be made. By extrapolating the straight line portion of the stool specific activity plot toward zero time, the endogenous Ca^{45} of this period was estimated to be 3 percent of the dose; therefore, 57 percent passed unabsorbed and 43 percent was utilized. For patient L utilization was calculated to be 67 percent. The results obtained by this method and independently by the ratio of specific activities are in close agreement.

The endogenous fecal calcium is total digestive juice (T.D.J.) calcium minus reabsorbed digestive juice calcium. The T.D.J. calcium may be estimated by

$$\frac{\text{T.D.J. Ca}}{\text{Food Ca} + \text{T.D.J. Ca}} = \frac{\text{specific activity of stool}}{\text{specific activity of plasma}}.$$

This estimation assumes that the calcium of food mixes homogenously and exchanges with the radiocalcium of digestive juices and thereby dilutes its specific activity, which was initially the same as that of the plasma. The absorption then proceeds from this homogenous mixture of food and digestive juice calcium, the nonabsorbed portion, that is, endogenous fecal calcium plus unabsorbed food calcium, being excreted in stool. Since the amount of food calcium and the specific activities of plasma and stool can be measured, the total digestive juice calcium can be calculated: 160 mg/day for B, and 370 mg/day for L. Both values are somewhat lower than the estimates, based on the estimated total volume of intestinal juices and their calcium concentration: 400 to 500 mg/day. However, if dietary calcium were absorbed before mixing with digestive juices or if exchange would take place across the intestinal wall, the T.D.J. calcium would be even lower.

Thus, by simultaneous measurements of Ca^{45} and metabolic balances, it is possible to measure the utilization of ingested calcium, its speed of absorption from the intestinal tract, and excretion and reabsorption of calcium of the digestive juices. This technique has also been used to measure the utilization of dietary calcium at various intake levels and to study the calcium compartments of the body in normal and pathologic states. These data will be reported separately.

Table 1. Metabolic balances.

	Patient B				Patient L			
	Nitrogen (mg/day)	Phosphorus (mg/day)	Calcium (mg/day)	Ca^{45}* (% dose)	Nitrogen (mg/day)	Phosphorus (mg/day)	Calcium (mg/day)	Ca^{45}* (% dose)
Intake	8990	534	107	100	11250	676	135	100
Urine	5120	269	90 ± 16	7.0	8150	366	51 ± 8	4.1
Stool	910	153	151	62.6	1100	225	162	42.3
Balance	+2960	+112	−134	30.4†	+ 2000	+ 85	− 78	53.6‡

* At end of experiment (26 days). † < 0.12 percent in the total plasma volume. ‡ < 0.20 percent in the total plasma volume.

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7 September 1954.

Partition of Neuraminic Acid among Human Serum Proteins

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Ever since the original description by Klenk, neuraminic acid has been recognized as a constituent of gangliosides (*1, 2*), and the specific color reaction that it gives with Bial's reagent (*3*) has been used to distinguish gangliosides from other water-soluble glycolipids (*4*). Neuraminic acid has been shown to be a constituent of gangliosides not only in lipid storage diseases (*1*), but also in normal mammalian nerve tissue, liver, spleen, and erythrocytes (*2, 5*). Attempts to demonstrate neuraminic acid in serum had, however, failed until recently, when Bohm *et al.* (*6*) showed that neuraminic acid was bound to serum proteins. Precipitation of serum proteins with trichloroacetic acid and subsequent treatment of the precipitate with Bial's reagent gave the characteristic Klenk-Langerbeins reaction for neuraminic acid. Since these workers were also able to isolate neuraminic acid from serum, the presence of neuraminic acid in serum appears established.

Our own attempts were directed at determining to which of the serum protein fractions neuraminic acid is normally bound (*7*). Fresh human serums obtained from (i) individual subjects, (ii) random hospital patients (10 pooled), and (iii) American Red Cross blood donors (40 pooled) showed neuraminic acid values ranging between 440 and 496 μg/ml serum according to the procedure of Bohm *et al.* (*6*). That the binding of neuraminic acid to certain of the serum proteins exists independent of a coprecipitation phenomenon which might arise in the course of trichloroacetic acid precipitation of proteins was confirmed by pressure ultrafiltration of serum. The ultrafiltrate contained no neuraminic acid. Treatment of the trichloroacetic acid precipitates with boiling ethanol and chloroform-methanol (2:1) did not extract neuraminic acid from the protein moiety.

Electrophoretic separation of serum proteins was undertaken with a Durrum-type paper electrophoresis apparatus, using 0.05*M* diethylbarbiturate buffer at *p*H 8.64 and a potential difference gradient of 15 v/cm. The paper was Whatman No. 1 with a strip width of 3.7 cm. In order to effect clearing of the starting point by the gamma-globulin zone, the serum was applied 4 cm away from the center (apex) toward the cathode. Four strips each carrying 20 μlit of serum were used in each run. After allowing electrophoretic separation of the zones to proceed for 6 to 8 hr, a guide strip was oven-dried and stained with bromphenol-blue in the usual manner. The untreated strips that were to be analyzed for neuraminic acid were not allowed to dry. Segments corresponding to the albumin, alpha-1 globulins, alpha-2 globulins, beta and gamma globulins, as well as the line of origin, were carefully cut out. The respective segments from three or four strips were combined and extracted overnight with distilled water. The aqueous extracts were individually lyophilized and analyzed for neuraminic acid by the modified procedure of Bohm *et al.* (*6*).

The results of the analyses indicate (Fig. 1, Table 1) that the maximum amount of neuraminic acid in human serum is located in the alpha-2 globulin fraction. The lesser amounts found in the alpha-1 and beta-globulin segments can be ascribed to the fact that portions of these fractions are overlapped by the edges of the alpha-2 globulin zone. The same preponderance of neuraminic acid in the alpha 2 globulin fraction was found in individual serums as well as in pooled serums from 10 hospital patients and also from 40 normal blood donors.

When the serum proteins were precipitated with 10 vol of ethanol, redissolved in 0.9 percent saline, and

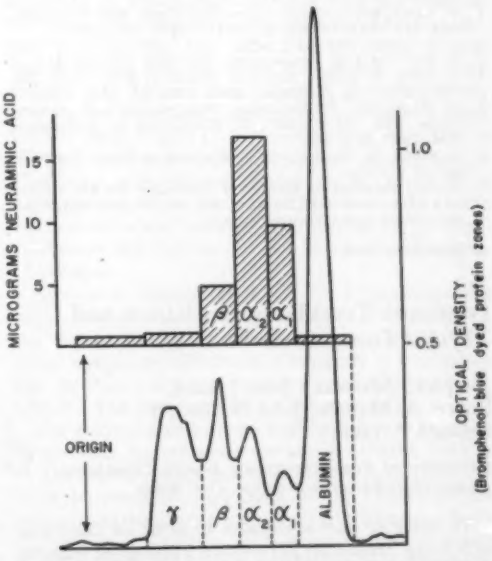

Fig. 1. Distribution of neuraminic acid with respect to serum proteins on electropherograms. The scanning of the bromphenol-blue-dyed protein zones represents a strip with 20-μlit serum. The neuraminic acid values correspond to four such strips (80-μlit serum).

Table 1. Neuraminic acid values (in micrograms) for different zones of paper electropherograms.
(80 μlit serum)

Serums	Albumin	Globulins				Starting point
		alpha-1	alpha-2	beta	gamma	
Single case	0.6	7.8	12.0	2.4	2.0	1.0
10 patients (pooled)	.7	9.6	16.8	4.8	0.8	0.8
40 normal adult males (pooled)	.9	7.5	14.5	7.0	3.0	1.3

heated for 30 min in a boiling water bath and then reprecipitated with 8 vol of ethanol, neuraminic acid was released and could be detected in the alcoholic supernatant about 80 percent of total originally present). Since this procedure is unlikely to result in hydrolysis of a polysaccharide or glycolipid, it appears unlikely that neuraminic acid is a constituent of an independent polymer that happens to have the same mobility as alpha-2 globulins; rather it indicates that neuraminic acid is either bound to alpha-2 globulins or is present as a constituent of the polysaccharide or glycolipid moieties of alpha-2 globulins. The relationship of neuraminic acid levels to alpha-2 globulin levels in various disease states is under investigation.

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* Captain, MC, AUS.
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10 September 1954.

Fractional Total-Body Irradiation and Thyroid Function in the Burro

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Thyroids of burros exposed to acute or fractional total-body irradiation have shown histological evidence of extreme stimulation by hyperplasia of the epithelial cells and marked colloid depletion.

Increased uptake of iodine-131 in thyroids of irradiated animals has been reported by Monroe *et al.* (*1*), Evans *et al.* (*2*), and Hursh *et al.* (*3*). Botkin *et al.* (*4*), however, noted that total-body irradiated rats had a decrease that followed a small initial rise. In the present study (*5*) burros were exposed to total-body cobalt-60 gamma irradiation, 25 r/day, until death and the thyroid uptake of intraperitoneally administered iodine-131 (*6*) followed.

Of 13 healthy burros (*Equus asinus asinus*), ten were simultaneously exposed, and three served as controls for stable iodine determinations (*7*). Exposures were made on a large exposure field previously described (*8*). Burros were allowed orchard grass hay, water, and noniodized salt *ad libitum* throughout the study. Each animal was its own control, by comparison with preirradiation rate of uptake. To increase the number of observations, the group was divided and, at staggered intervals, each group of five received intraperitoneal injections of 10 μc of carrier free iodine-131. Thyroid activity was measured by external counting with a scintillation counter (NaI crystal). The iodine-131 that accumulated in the thyroid 8 hr after injection was chosen for purposes of comparison. The fractionation and determination of total stable iodine and stable thyroxin iodine were done by the method of Taurog and Chaikoff (*9*).

After 600 to 800 r some animals began to concentrate iodine-131 (Fig. 1*b*) to a marked degree; others

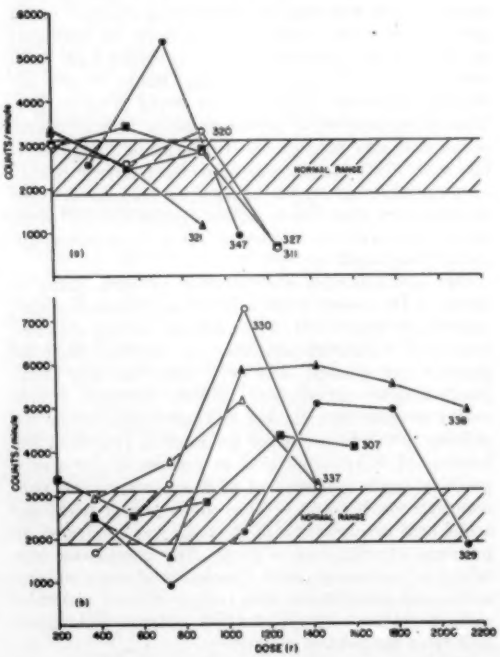

Fig. 1. Counts per minute over the thyroid at various accumulated dose levels. The plots are separated for ease in reading.

Table 1. Ratios and amounts of total stable iodine and total stable thyroxin iodine in the thyroid glands of burros at death (mg/g). Mean ± standard error.

	Group Ia	Group Ib	Control
Survival (days)	49.5 ± 1.23	79.0 ± 4.66	
Total iodine (TI)	6.4 ± 2.8	1.20 ± 0.22	5.56 ± 1.98
Thyroxin (TX) iodine	0.70 ± 0.27	0.24 ± .44	0.66 ± 0.22
TX/TI	.127 ± .021	.212 ± .044	.133 ± .028

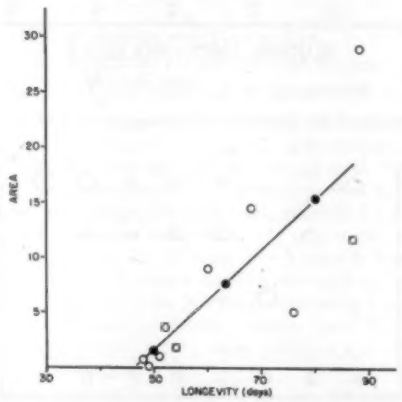

Fig. 2 Planometrically determined areas beneath the curves in Fig. 1*a* and *b*, expressed in arbitrary units, as a function of survival time. The black dots and connecting line represent the regression of area on longevity.

fell to subnormal levels (Fig. 1*a*). Those that accumulated iodine-131 survived significantly longer than did those within the normal range or below.

This relationship was not observed in the stable iodine values of thyroids taken at autopsy. The total stable iodine and the stable thyroxin iodine was least in those surviving the longest. In those surviving the shortest period of time both the stable iodine content and thyroxin iodine content were not significantly different from the normal controls (Table 1).

A significant correlation was apparent between the planometrically determined areas under the accumulation curves (Fig. 1*a* and *b*) and the survival time of the animals (Fig. 2).

The causal relationship between iodine-131 uptake and survival is not understood. It may be a reflection of degree of stress response to ionizing radiation. The early deaths may indicate a body-wide metabolic collapse, whereas later deaths indicate less irreparable damage and partial compensation for injury but eventual deaths from more latent physiologic disturbances.

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30 August 1954.

Demonstration of an Oligosaccharide Intermediate in the Enzymatic Hydrolysis of Cellulose

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Data summarized by Reese *et al.* (*1*), and Tracey (*2*) indicate a random cleavage of the cellulose molecule by cellulase. Such a random cleavage should yield a variety of intermediate dextrins with the eventual formation of cellobiose and glucose. However, the only products that have been found, in spite of concerted efforts, are cellobiose and glucose (*3*). This failure, plus the fact that cellobiose, but not glucose, inhibits the enzymatic hydrolysis of cellulose (*1*), has led Levinson *et al.* (*4*) to conclude that cellobiose is the end-product of cellulase action, in analogy to β-amylase, with glucose arising as the result of a β-glucosidase. This communication is to report the demonstration and tentative identification of an oligosaccharide intermediate in the enzymatic hydrolysis of cellulose.

Successful demonstration of the intermediate has been achieved repeatedly by enhanced dissociation of the oligosaccharide-enzyme complex through dialysis. After incubating cellulase and substrate in a collodion sac, an oligosaccharide, tentatively identified as cellotetraose, was demonstrated in the dialyzate.

The enzyme used in these experiments was obtained by growing *Myrothecium verrucaria* (USDA 1334.2) on the medium of Saunders *et al.* (*5*) for 11 days at room temperature. Two liters of the culture filtrate was concentrated in vacuum to 50 ml and exhaustively dialyzed in a collodion sac against running tap and distilled water. No further purification was attempted. The cellulose substrate (Solka-floc) was swollen in phosphoric acid by the method of Walseth (*6*) and also dialyzed against tap and distilled water.

Two grams of substrate, suspended in 45 ml of distilled water, was placed in a freshly prepared collodion sac with 2 mg of dialyzed Difco proteose-peptone (*7*) and 5 ml of the concentrated enzyme solution. The collodion sac was suspended in 2 lit of 0.001*M* acetate buffer, *p*H 5.0. The external and internal solutions were stirred continuously at 50°C for 5 hr.

The dialyzate was concentrated to 10 ml in vacuum, and chromatographed on Whatman No. 1 filter paper using an isopropyl alcohol, water, and glacial acetic acid solvent (*4*). The chromatograms when developed with a benzidine spray (*8*) indicated large concentrations of glucose and cellobiose and the presence of another reducing sugar with a lower R_F. Five milliliters of the concentrate was strip-chromatographed in the afore-mentioned solvent, and reference strips were developed with the benzidine spray. The sections of the unsprayed chromatogram that the reference strips indicated to contain the higher saccharide were cut out and eluted with water. The eluate was concentrated in vacuum to 5 ml and rechromatographed. These chromatograms indicated the presence of a single reducing sugar. Control experiments of cellulose or enzyme alone failed to give rise to the observed higher saccharide. R_F values are given in Table 1.

Total sugars were determined as glucose by the anthrone method of Dimler *et al.* (*9*) and reducing sugars by the methods of Somogyi (*10*) and Nelson (*11*). The molar concentration of the saccharide was determined by comparing its reducing power with cellobiose rather than with glucose (*12*). From the molar concentration the molecular weight was calculated to be 635 (including corrections for the addition of water and filter paper blanks) as compared with a theoretical 666 for cellotetraose. This error of less than 5 percent is considered to be within the limits of the methods used. Further evidence that the new compound is the tetraose is the fact that when the R_M values (*13*) are plotted as a function of the number of glucose units per molecule, a straight line results (Fig. 1).

Evidence that the oligosaccharide is an intermediate in the hydrolysis of cellulose was obtained by incubating 1.0 ml of sugar solution containing 448 μg with 0.1 ml of the concentrated enzyme at 50°C. Samples were withdrawn periodically and chromatographed in solvent B with the results shown in Fig. 2.

Since only very limited quantities (about 2 mg) of the oligosaccharide were available for study, positive identification must await the isolation of larger amounts.

It should be noted that after the developed chromatograms stood for several hours traces of an unidentified substance appeared midway between glucose and cellobiose. This spot gave a green color reaction with benzidine rather than the characteristic brown of reducing sugars. Eluates of this substance gave a negative reaction with both the anthrone and the Somogyi reagent. This substance was also present in a hydrochloric acid hydrolyzate of cellulose.

The significance of this demonstration is that it gives form and substance to the random cleavage hypothesis (*14*). Further investigations and complete characterization of this and other intermediates are in progress.

Table 1. R_F values of the observed hydrolytic products of cellulose.

Sugar	Solvents*		
	A	B	C
Glucose	0.47	0.54	0.74
Cellobiose	.29	.41	.66
Higher saccharide	.08	.19	.45

* The solvents consisted of glacial acetic acid, isopropyl alcohol and water in the following ratios (V/V/V): A (10 : 67.5 : 22.5); B (10 : 58.5 : 31.5); C (10 : 49.5 : 40.5).

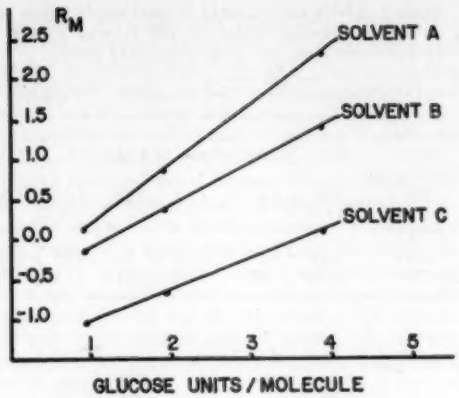

Fig. 1. Relationship of R_M values, $1n(\frac{1}{R_F}-1)$ and molecular size of the observed hydrolytic products of cellulose.

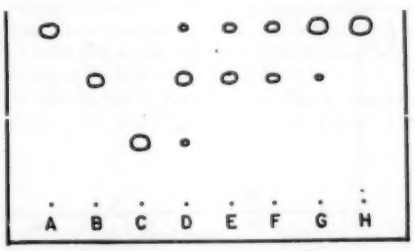

Fig. 2. Chromatographic analysis of oligosaccharide hydrolysis: *A*, known glucose; *B*, known cellobiose; *C*, oligosaccharide plus enzyme, 0 min; *D*, 10 min; *E*, 30 min; *F*, 60 min; *G*, 120 min; *H*, 240 min.

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Hydrogen Bonding in 7-Ketocholesterol and a New Isomorph of 7-Ketocholesteryl Acetate

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In 1946 Furchgott, Rosenkrantz, and Shorr (*1*), employing infrared techniques, demonstrated that many steroids undergo hydrogen bonding in the solid state. This phenomenon has been observed, not only for the physiologically important steroids (*1, 2*), but also for ergostane compounds (*3*) and in the cholesterol series (*4*). In all cases one hydroxyl band occurred and the hydrogen bonding was evident because of displacement of the hydroxyl stretching vibrations from the unassociated wave number near 3640 cm^{-1} (wavelength, 2.75 μ) to wave numbers nearer 3330 cm^{-1} (wavelength, 3 μ).

During the infrared studies on the cholestane derivatives (*4*), it was observed that only 7-ketocholesterol gave rise to two absorption bands in the hydroxyl region. This occurred in the spectra of solid films, Nujol mulls, carbon disulfide (10 mg/ml, 1-mm cell) and carbon tetrachloride (5 mg/ml, 2-mm cell) solutions. In the solid state both bands were nearly of equal intensity, the sharper one occurring near 3545 cm^{-1} (wavelength 2.82 μ), while a broader one was located near 3280 cm^{-1} (wavelength 3.05 μ). In the solutions the usual increase in wave number owing to this state was observed, 3615 cm^{-1} (wavelength 2.77 μ) and 3417 cm^{-1} (wavelength 2.93 μ), respectively. No significant displacement of the ketone absorption occurred either in the solid state or in solution.

A doublet in the hydroxyl region was observed by Jones *et al.* (*2*) in the spectra of 17α-hydroxy-20-ketosteroids. Intramolecular hydrogen bonding was proposed as an explanation for the hydroxyl doublet, and it was reported that a threefold dilution in carbon tetrachloride did not alter the relative intensities of the two hydroxyl bands. Splitting of the normal 20-ketone absorption band was interpreted as indicative of an equilibrium between bonded and unbonded molecules. One other instance of the appearance of a doublet in the 3-μ region has been reported for cholestane-3β,5α-diol-6-one (*5*).

Dilution of a solute involved in hydrogen bonding is known to decrease the intensity of the associated absorption band and increase that of the higher frequency band. In the present study (*6*) a twofold or threefold dilution in carbon tetrachloride or carbon disulfide did not alter the relative intensities of the two hydroxyl bands. Before postulating hydrogen bonding for the origin of the 3-μ doublet, the possibility of tautomerism was examined by attempting to synthesize the enol acetate of 7-ketocholesterol. On refluxing 7-ketocholesteryl acetate with acetic anhydride and acetyl chloride, $\Delta^{3,5}$-cholestadiene-7-one (*7*) was obtained in 25-percent yield. The structure was established by infrared analysis, melting point 110° to 112°C, and elemental analysis: found C, 84.52; H, 10.90; calculated C, 84.75; H, 11.07. Treatment with acetic anhydride and sodium acetate or with acetic anhydride and pyridine resulted in formation of a dimorph (mp 163° to 164°C; found C, 78.57; H, 10.41; calculated C, 78.68; H, 10.47) of the starting material (mp 153° to 155°C). The lower melting modification could be transformed into the higher melting form by seeding its pyridine solution with crystals of the new isomorph. Both compounds gave identical infrared spectra in carbon disulfide solution (10 mg/ml; 1-mm cell; 12 C Perkin-Elmer infrared spectrometer).

Ultraviolet spectroscopic analysis was also employed in an attempt to estimate quantitatively any possible enol structure. If 7-ketocholesteryl acetate enolized, then either a $\Delta^{5,7}$-diene or a more stable $\Delta^{4,6}$-diene would arise. The absorption of the latter arrangement cannot be distinguished from the 240-mμ absorption of the parent molecule, but the $\Delta^{5,7}$-structure absorbs near 285 mμ. Therefore, although variation in the density at 240 mμ could not be interpreted, appearance of a maximum near 285 mμ could favor the formation of the $\Delta^{5,7}$-diene intermediate.

7-Ketocholesteryl acetate was studied in neutral (isooctane), acidic (acetic anhydride plus acetyl chloride) and basic (0.07*N* tetramethylammonium hydroxide in 90-percent ethanol) solutions [method of A. S. Meyer, personal communication] in a 1-cm cell at concentrations of 20 μg/ml. Either a Beckman DU or Cary 11 MS spectrophotometer was used for the determinations at zero, 4 and 24 hr.

No absorption occurred under neutral or acidic conditions, while a maximum near 285 mμ in the basic medium could account for approximately 20 percent intermediate. Whether this 285-mμ maximum is related to the $\Delta^{5,7}$-diene structure under the basic conditions used remains to be seen, but it should be recalled that enol acetate formation is catalized by acids.

Failure to prepare the enol acetate of 7-ketocholesterol by the usual chemical means in addition to the ultraviolet findings indicated that tautomerism did not significantly occur in this molecule. Therefore, the origin of the two absorption bands in the hydroxyl region have been assigned to an unusual tendency of intermolecular hydrogen bonding in 7-ketocholesterol. Indeed, this phenomenon may explain the difficulty in synthesizing the enol acetate of 7-ketocholesterol. Ad-

ditional evidence for the possible interference of hydrogen bonding with enolization was obtained from attempts to synthesize the enol acetate of cholestane-3β,5α-diol-6-one which has been shown to give a doublet in the 3-μ region (*5*). On refluxing this steroid with acetic anhydride and acetyl chloride, only the 3,5-diacetate was isolated in excellent yield (*8*).

Although variations in the carbonyl absorption did not occur, it is believed that a hydroxyl-ketone type bonding was prevalent. This was indicated by examination of the spectrum of 7-ketocholestanol which had only one absorption band in the 3-μ region (*4*) and suggested that the double bond in the unsaturated analog afforded a more rigid structure that favored bonding of the carbonyl group. As expected, the infrared spectrum of 7-ketocholesteryl acetate gave no absorption bands in the hydroxyl region, confirming that the 3β-hydroxyl group also was involved in the hydrogen bonding. Furthermore, spectroscopic examination of 7β-hydroxycholestenone (*9*) disclosed only one hydroxyl band and fortified the interpretation that 7-ketocholesterol had a more favorable steric arrangement for hydrogen bonding than compounds that have similar functional groups at other positions.

It is suggested that difficulty in synthesizing enol acetates be examined on the basis of the possibility and intensity of hydrogen bonding.

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6 August 1954.

Communications

Big Business and Research

Although I am loath to engage in public controversy, Philip Reichert's communication [*Science* **120**, 434 (1954)] requires an answer. Reichert emphasizes that the university professor has as his first function education rather than the performance of research. This definition is one with which others might disagree, since there is considerable support in the history of universities for their function as centers of learning in which education of disciples and free investigation of ideas or objective observations have equal importance.

The application of business methods to research has resulted in "a flood of immediately practical therapy" without any doubt. However, the great advance in basic knowledge upon which the practical applications must be based have rarely resulted from business methods in research. Business is fundamentally interested in profit, and therefore it is axiomatic that the research must be directed toward a profitable end. Even the "basic research" supported by business is of limited scope and usually is directed toward the solution of some project that has business interest. To any scientist who has dealt with the research performed in business organizations, or who has attempted to find money for basic research in grants from business organizations, the truth of my statements must be obvious. I base them upon my own experiences in this regard.

"The widespread distribution of information on new medical products" is a plague of the medical profession. The information is never unbiased (well, hardly ever!). Motivation need not be questioned. The results are evident in the pounds of "continuing postgraduate courses" that cross my desk daily. Several examples lie before me as I write, published by "ethical pharmaceutical" concerns, in which recommendations are made as though they were based upon incontrovertible fact, whereas these recommendations, in truth, either are directly contrary to the majority opinion among responsible investigators or are the subject of raging controversy.

"From the point of view of the patient—the average citizen—," he had better depend on physicians who form their opinions independently, from sources of information that are divorced from the immediate pressure of financial interest.

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6 October 1954.

In so far as R. W. Lippman's conclusions are based upon his own experiences, his conclusions are naturally valid for him. As a researcher who has crossed to the other side of the desk, I have during the last 10 years assisted in distributing many thousands of dollars in grants to approximately 20 first-line investigators. None of these men seem to be hampered by the fact that they are working for organizations that have a profit motive.

The difference between business research and university research is largely the pressure of the time element, and this usually means that the grants are

generous so that time can be saved and additional help provided for the investigator.

One point that needs careful consideration is the traditional attitude of suspicion and derogation which Lippman shares with the medical profession generally —that "profit motive" is synonymous with bias and dishonesty. To begin with, the profit motive is psychologically the most powerful incentive to any activity, and let us agree that the profit motive and the free enterprise system under which we live have not done too badly for us.

If I may use my own direct experience, as Lippman uses his, I should like to go back to 1946 when I was intimately connected with the promotional drive behind penicillin, a new drug then, and in fact a new concept in medicine. I remember that 100,000 units of the amorphous material sold for $20, when it could be obtained at all. Competition at that time was very strong, and research into methods of production, control, and packaging bordered on the hysterical. Today, 1 million units of crystalline penicillin can be purchased in any drug store in the United States for about 40 ct.

We cannot make a comparison with the $20 price of 1946 because 100,000 units today, which are sold for approximately 10 ct, cannot be compared as a product, since no one today would think of selling the crude amorphous penicillin. It is true that the basic research that produced penicillin was done in a university hospital, but it is also true that it languished on a shelf there for a decade. It was only when the profit motive entered the picture that this kind of progress was possible. The most miraculous drug is of little value until the physician at the bedside has the actual package in his hand, and if it is the "pressure of financial interest" that puts it there, let us at least appreciate the part that it takes in the lifesaving picture.

I referred briefly to "packaging." The 1946 amorphous penicillin was outdated in a matter of weeks. Present-day penicillin may be dated 2 years ahead. The intensive (and expensive) work of the first-class pharmacological and production engineers that went into this one aspect alone is never given a passing thought by the man who is the most benefited by such a detail, the man who opens the package at the bedside.

This is no isolated case. I lived through the same pattern with the synthesis of vitamin C, with the steroid hormones, with the wide spectrum antibiotics, and now with the *Rauwolfia* products.

Lippman's opinion that the "widespread distribution of information on new medical products" is a "plague" is again a traditional attitude that for the sake of American medical progress definitely needs changing. Big business has learned the hard fact that bias does not pay off. The profit motive itself makes for honesty, because the largest profit always goes to the man who best satisfies a human need.

"Recommendations [that] . . . are directly contrary to the majority opinion among responsible investigators" would have an F.D.A. citation so fast that the medical director of the company involved would be looking for another job that same week. I think it important that more physicians know how closely the government agencies scrutinize the labeling and brochures on pharmaceutical products. It is just impossible to make a claim unless it is well supported by investigators of unimpeachable reputation.

I have been increasingly proud of the organizations that have eagerly hunted out the discoveries that showed promise, distributed them to teams of trained investigators under grants, and so reduced the lag between laboratory bench and bedside. This pattern of research is no longer new and untried. It would not work if investigators did not want it to work, since it depends on men as well as on money.

The "talent scouts" of big business are a new profession; they might be called "medical expediters." Big business has learned to rely on, and to pay for, only the best-trained medical specialists. No management wants to risk its reputation and its capital on a gamble with truth, and nothing sells so well as a pharmaceutical product that really lives up to its claims.

The "profit motive" is under attack from many quarters of the world; I wish it were not so fashionable for those of us who live under it and benefit from such an economy thoughtlessly to add fuel to this attack. The attitude of automatically suspecting everything with a profit motive as having inherent bias is completely unrealistic. Let me cite two examples of what I meant by the "continuing postgraduate course."

1) At least twice a month every physician in America receives, at no cost whatever, a number of digest magazines. One of them in particular is edited by one of the best-loved and most impressive figures in American medicine. His list of editorial assistants and consultants reads like a roll call of the most honorable names in our profession. This is a "profit motive" job. Any physician that follows it carefully from month to month will have enough material on which he can form his opinions independently.

2) One of the most useful and informative of educational methods, as well as the most expensive, is the medical motion picture. There is hardly a field in modern medicine in which there does not exist, sponsored by a profit-making company, a competent and interesting motion picture, always produced under the direction of a great name in that specialty. Booking these for a medical meeting is usually free, or there is a very nominal shipping charge.

These are parts of the "continuing postgraduate" education to which I referred. Their integrity and lack of bias are guaranteed by the prominence of the professional names behind them. The entire cost of such projects as these is underwritten by commercial houses; their motivation is not hidden, nor can I see it as evil.

That there is a change from the traditional attitudes of medicine is nowhere better exemplified than in a pamphlet received this very morning from my own county medical society on *Guidance for Medical Co-*

operation with Public Press, TV and Radio. Many of the practices that as recently as 5 years ago would have landed a practitioner before his ethics committee are now not only permitted but encouraged. Programs of the learned societies have speakers and discussants from universities and hospitals side by side with workers from the pharmaceutical companies' research laboratories. Major investigators freely acknowledge by footnote the support of commercial grants.

In brief, if research is dominated by big business with all its great resources, its drive toward the practical, its profit motive, let us realize also that its life blood and success are a sober recognition of the value of top names, top people, top authority, top quality of work. The bigger the business, the more certain can you be that it has grown through the complete realization that honesty pays off! This pattern is completely typical of the pattern of our entire economy and is one of the most potent proofs of its value.

The next time any one of our physician leaders gives an injection of his 40-ct penicillin, I hope he will look at it and visualize the business that made it possible for him to have it. Maybe we should try to throw off the shackles of some of our traditional attitudes and try to examine the activities of big business with the same detached and objective evaluation that we habitually give to our test-tube and laboratory bench work.

PHILIP REICHERT

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4 November 1954.

R. W. Lippman is a practicing physician who also is engaged in research; he is a former fellow of the John Simon Guggenheim Memorial Foundation. Philip Reichert, ex-Rockefeller Institute, and still maintaining a consulting practice in cardiology, is currently director in a large advertising agency of a division that prepares promotional material directed to the medical, dental, and auxiliary professions.

Forms for Literature Citations

McCasland's proposed telegraphic system of literature citation [Science **120**, 150 (1954)] would certainly be convenient for compilers of bibliographies. I should like to consider it from the point of view of the users of bibliographies. What does the user want from a reference? Unless he is merely engaged in the reprehensible practice of copying it into a bibliography of his own, he wants to find out more about what the cited paper contains. To do this, he must consult either the original paper or, if this is not possible, an abstracting journal. In the latter case the author's name is essential, and, therefore, since not all libraries receive all journals, McCasland's suggestion of eventually omitting the author's name seems impractical. If the original paper is to be consulted, a minimum reference would seem quite satisfactory.

Here, however, we come up against the fact, well known in communication theory, that a message which is subject to distortion by "noise" must contain an appreciable amount of redundancy if its meaning is to be sure of surviving. When the message is a citation, the noise is furnished by the bibliographer's mistakes, his secretary's errors in transcription, the printer's errors, and even the blunders of well-intentioned editorial assistants. Actual experience in checking thousands of literature citations made by professional mathematicians has shown that these sources of noise are quite serious. The commonest mistake is a one-digit error in a date or a volume number; more baffling problems arise when the author writes, for instance, *Math. Z.* when he intends *Math. Ann.* In such cases redundancy saves the day: it is easy to find out whether the impossible **12** (1936) really means **22** (1936) or **12** (1926). Again, since volume 56 of *Math. Z.* was roughly contemporaneous with volume 125 of *Math. Ann.*, it is easy to decide, given both volume and date, which journal was intended.

A four-letter code for the journal name suffers badly from lack of redundancy. A single garbled letter may make the name unintelligible or even impossible to reconstruct. An abbreviation like *Trans. Am. Math. Soc.* is recognizable even with several bibliographer's or printer's errors, while **AMST** is not. Experience again shows that authors are rather careless in writing abbreviations of journal names. This particular one would probably frequently come out **TAMS:** the transposition would be obvious to an alert reader, but hardly so to an automatic sorting device.

Some apparently redundant items are not really redundant, and are likely to remain indispensable until that millennial day when all editors of journals do just what McCasland recommends. The year does not always determine the series: there are journals that have started series 3 before completing series 2. There are also journals that have appeared several years later than their dates or (more remarkably) before their dates. Since it is sometimes desirable to know in what year a paper actually appeared, it would be helpful if the present citation system were on occasion extended (rather than contracted) to indicate both the official date and the actual date of publication.

I even hope for one other expansion in citations, namely the citing of inclusive pages. This is now customary in mathematical journals, and there are several good reasons for it. One is that if one wants to order a microfilm or photostat copy, one needs to know in advance how long the paper is.

In general, it would seem that citations are already so brief that little space could be saved by shortening them still more, whereas any further compression is against the interests of the people who use the citations and for whose benefit they presumably are intended.

R. P. BOAS, JR.

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3 August 1954.

The recent communication by G. E. McCasland (*1*) concerning condensed literature citations will, I hope, provoke general discussion. Similar proposals have been advanced before (*2*), and it seems likely that such a condensation *could* be carried out, but *should* it?

These and similar proposals contemplate using sets of alpha-numeric characters having essentially zero redundancy. This means that if any single character is wrong, the citation is lost.

Hundreds of years of experience have gone into vernacular languages which show a high degree of redundancy (*3*) and this is reflected in current methods of literature citation. Should not this fund of experience continue to guide decisions that affect scientists so directly?

The situation at present is bad enough, mainly because of the older practices in abbreviation and citation. McKeehan (*4*) has some pertinent remarks on this subject.

> Everybody in this business, and especially every editor, tries to compress references into minimum space. This often makes them not merely incomplete but tantalizing also. It is much better from our present point of view to be redundant rather than cryptic. If there are several clues . . . the chance of losing everything by one wild misprint is very much reduced. In any one period the scientific public may easily recognize an abbreviation . . . but, as time goes on, styles change, and it needs hard work to win back the discarded details. The references in a fine treatise published in 1867 are now a series of puzzles because of elisions and abbreviations that were probably clear enough to early readers.

Dyson (*5*) gives some entries under "Iodine" from the Gmelin-Watts translation that are quite unfamiliar and these also contain no indication of date.

The subject of periodical abbreviations has been treated recently (*6*).

Finally, anyone who has read the excellent review of *A Bibliography of the Research in Tissue Culture: 1884 to 1950*, made by P. R. White (*7*) can have only the greatest respect for the compilers, Murray and Kopech. They had 5500 ghost references for 20,000 actually found and used! Any practice that might tend to increase this figure should be examined carefully before adoption.

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2 September 1954.

Table 1. Three proposed forms for literature citations.

Proposer	Name	Example	Remarks
McCasland		799-**AJBC**-48.3	First letter of journal abbreviation has geographic significance
Reid	Sigil	48 JBC 3, 799	Number of letters in journal abbreviation not fixed
Bishop	Coden	JBCH-173-799 or 48JBCH-173-799	Prefixing of year is optional

In the 23 July 1954 issue of *Science*, G. E. McCasland proposed that scientific literature be cited by a concise designation that includes the page number, an arbitrary four-letter abbreviation for the journal, the year and part of the volume number where necessary. I made a similar proposal in *American Documentation* 4, 54 (1953). Since then I have prepared a separate list of approximately 2500 journal abbreviations, which I have distributed informally. As a result of this, the Committee on Spectral Absorption Data and the A.S.T.M. Committee E-13 on Absorption Spectroscopy have asked and been granted permission to use the system on their keysort file of 13,000 compounds. Several other groups have indicated that they are trying the system. Thus as McCasland suggests, the idea of a concise and direct literature citation has considerable utility.

My "coden" differs slightly from the form proposed by McCasland in that I cite full volume number and no year. Also, my journal abbreviation is completely arbitrary but mnemonic wherever possible. The year can be incorporated if desired by prefixing it. Combining the year and part of the volume number as McCasland suggests is similar to the practice of J. B. Reid [*American Documentation* 5, 26 (1954)], who lists year, journal abbreviation, last digit of volume number if necessary, and page. Reid points out that by citing the year first, one automatically throws the references into chronological order. Table 1 shows how the proposed forms will be applied to an article in *Journal of Biological Chemistry*, volume 173, page 799, year 1948.

Regardless of the form used a direct, concise method of citation has many uses. One is in organizing bibliographies or review articles, for articles can be added or withdrawn without altering an arbitrarily numbered list of references. Furthermore, two bibliographies can be combined with the automatic elimination of duplicates. In our laboratory we prepare 3- by 5-in. reference cards using the coden, authors, title, number of pages, and year. All the cards constituting one bibliography are laid out and photographed. The cards are then returned to the "coden" file and brought out in a different combination for the next

bibliography. A bibliography on any subject can be prepared rapidly and with no subsequent errors, once the original cards are error-free. We use the same cards to prepare tables of contents of journals; and we find this quite a time-saver.

It appears that several people have independently "discovered" the merits of a concise literature citation. If such a designation could be made universal, a great deal of duplicated effort in bibliography could be avoided. Perhaps the first step is to agree on the exact form of the citation. Then the list of standard journal abbreviations should be compiled and published. This latter task is too time consuming for one individual to accomplish but would not seem anything more than a routine chore for an organization that is processing journals continually. Once a list is published, everyone can reap the benefits of a concise, universal literature citation.

CHARLES BISHOP

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7 September 1954.

It is not entirely correct to assume that the "minimum information necessary in principle to specify a certain article" is the page, journal name, and year. Patents have long been identified by serial numbers. In theory, published articles could be so identified.

Another approach—different from Bishop's or Reid's—is to identify the individual article by a serial number of two parts: the first part identifying the journal, similar to the identifying numbers used in the *World List of Scientific Periodicals* or the *Bibliographie der Fremdsprachigen Zeitschriften Literatur*; the second part a serial number as exemplified by those used in the *Proc. Soc. Exptl. Biol. Med.* or the reprint order number in the *J. Chem. Soc.* (*London*). The serial number has its obvious disadvantages as would an approach based on the use of secondary publication references, such as the volume and column number in *Chemical Abstracts* or the numbers in publications like the *Current List of Medical Literature* and the *Bulletin Analytique*. The disadvantages increase as one gets further away from the original complete citation. Communication engineers face similar coding problems. Both brevity and redundancy have shortcomings.

It is necessary to determine the function of any proposed citation system. If a unique identification tag is all we require, then the patent system is enough. If the tag is to contain journal identification, then the two-part serial number is sufficient and far more desirable for punched-card applications, where the sorting of numbers is less time consuming than the sorting of letters. In "The preparation of printed indexes by automatic punched-card equipment—a manual of procedures" (*Medical Indexing Project Report*, Johns Hopkins Univ., Mar. 1953) I have demonstrated the feasibility of using such numerical identification tags for the compilation of scientific indexes.

If the tag is to have mnemonic, as well as classificatory features, then the difficulties increase. It is questionable whether the space saved by reducing the already abbreviated citations compensates for the time lost in trying to identify the citations in published articles. The retention of the journal title in the accepted abbreviated form will probably continue for many years, since most libraries must ultimately deal with the journal title, volume, page, and even year for verification. However, the *addition* to the established citation form of a unique tag such as a serial number would not be an excessively heavy burden on an author or editor. Such tags could help in speeding up communication between scientists and help particularly in facilitating the compilation of many types of compendiums, where uniqueness and brevity are compulsory.

EUGENE GARFIELD, *Documentation Consultant*
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13 September 1954.

When I wish to enlarge my knowledge on any subject, I go through a process that I call "browsing." My point of departure usually is a paper in my own library, and often it is not on the subject of interest but only treats it incidentally. However, study of the list of literature cited many times reveals at least one paper that *is* on the subject. I can recognize the paper by its title and judge the thoroughness of treatment by the number of pages included. If this information is omitted then each paper must be found and examined in the library in order to determine its nature.

The process would be still further slowed if a coded form, such as that proposed by McCasland, were adopted, for then it would be necessary to consult a code book, as well as the library, in order to learn what a paper is about and how comprehensive it is. I for one hope that journals giving full references will retain them and that those using abbreviations will not resort to coding.

The final step, of course, is the push-button information center envisioned by McCasland, which I shudder to contemplate. The quiet stacks of our libraries remain one of the few easily accessible refuges from modern, souped-up, gadget-ridden civilization. Must they too go?

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22 September 1954.

Those who oppose the abbreviated citations claim that an increase in errors would result. To enjoy the benefits of abbreviation, as we all do in one way or another, we must accept some increase in the risk of errors. Redundancy may protect against errors but is usually too expensive a protection for routine employment.

People who produce or use scientific literature should find a concise citation system useful, but anyone who is interested will need to balance the advantages against possible disadvantages for his particular purpose. In many cases it will be desirable to supplement the "minimum" citations, for example, by adding the authors' names.

G. E. McCasland

University of Toronto

22 September 1954.

Randomized Targets in Parapsychology

The report by Kendon Smith and Harry J. Canon on "A methodological refinement in the study of ESP, and negative findings" (*1*) is of interest in two respects. First, it reopens some questions about the use of random numbers in experimental work; and second, it challenges a series of experimental studies which for the most part have gone unchallenged. The central point at issue is whether properly safeguarded tests of extrasensory perception, in which stimulus materials are made by tables of "random numbers," are valid.

The authors state that some findings "raise the suspicion that tables of random numbers may not be entirely random; that such tables may, in some small degree, actually embody conventional preferred sequences of digits." So far as I know, absolute randomness has never been claimed, and it is theoretically difficult, in view of sampling theory, to see what the concept could mean. What is meant by preparing random numbers is that one takes pains that each digit be followed by each of the 10 digits in haphazard order. When, as is usually the case, hundreds of such digits are employed in making up "targets" for subjects to guess at, it is hard to see how such material, kept out of all known sources of knowledge of experimental subjects, could significantly coincide with the orders in which subjects make their guesses, except by a process that, by definition, is extrasensory. It is true and important that from time to time a subject may by chance alone call a few items that are related to the actual "target" order; and it is true that in *control* series, brief periods of such parallelism of subjects' calls with targets at which the subjects are *not* aiming is occasionally observed. This is what would be expected from the theory of probability. When one is dealing, as in the case of the Schmeidler experiments (*2*), with hundreds of thousands of experimental calls, it is hard to see what could be meant by saying that failure of randomness in the targets could be responsible for the positive findings consistently obtained in guessing experiments.

In the experimental work reported by Smith and Canon, there were two kinds of targets—a pair of squares in which the left-hand one was blackened, and a pair of squares in which the right-hand one was blackened. The only task for the subject was to guess in each case whether it was the left or the right square that was blackened. This seems to have been an unfortunate choice of target material, since earlier work suggests that the right-left dimension of choice often means little in the type of visual or kinesthetic imagination involved. At least with pictorial material, reversal from right to left, as in a mirror, has been reported (*3*). This is not to suggest that it occurred here; only that no conclusion can safely be drawn from this type of target. The task involved, moreover, in making a choice of one out of two appears from some experimental work (*4*) to be sometimes too insensitive to mobilize the interests and energies of subjects in such experiments; the choice of one out of five seems, as in the work of Soal and Rhine, to be a more sensitive and suitable procedure.

It is of interest to know that there was no significant difference in the scoring levels of those who believed in and those who disbelieved in the reality of paranormal phenomena. Unfortunately, the method chosen by the experimenters is one that makes it difficult to compare the present findings with those of the extensive earlier work reported on this problem.

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13 October 1954.

Slide Technique for Bacteriophage Typing of *Staphylococcus aureus*

The phage typing of *Staphylococcus aureus* has become a useful tool in epidemiology, particularly in tracing outbreaks of food poisoning. An agar-petri plate method for typing was devised by R. E. Williams and J. E. Rippon [*J. Hyg.* **50**, 320 (1952)]. An agar-slide method that is simpler and less expensive has been developed in this laboratory.

Twelve 14-mm paraffin rings are simultaneously placed on a serologic slide (2 by 3 in.) by means of an electric ring-making apparatus. (The slides are placed in wooden racks designed for the purpose. These racks may be stacked for convenience.) Nutrient agar (0.5 to 0.7 percent) that has been filtered is pipetted by an automatic serologic pipetting machine (cleaned but not sterilized) in approximately 0.2- to 0.25-ml quantities into each paraffin ring. The agar hardens immediately. One drop of a 24-hr nutrient broth culture of *Staphylococcus* from a 0.2-ml serologic pipette (approximately 0.03 ml) is placed on each agar convexity. The culture dries in 15 to 20 min. Then a similar drop of each phage to be tested is placed on each of the culture-on-agar preparations. After drying 15 to 20 min, each slide is placed in a sterile covered petri dish and incubated overnight at

30°C. The phage action is observed the following morning. The phage reactions on the agar slide are similar to those noted on the agar plate, varying degrees of activity being observed.

This method was used in comparison with that of Williams and Rippon for some 500 cultures. Since then an additional 500 cultures have been run with the slide method alone. The agar-slide method appears to have these advantages over the agar-plate method.

1) It is a less exacting technique. The plate method requires the use of very fine capillary pipettes, which are difficult to make and handle without breaking. Great care must be exercised in placing extremely small drops, approximately 0.01 ml, on the agar plate to avoid transferring culture from one plate to another and to avoid spreading of the drop over a larger area of the agar than is designated for it by markings on the bottom of the plate.

2) It takes less time to carry out the test with slides. Agar placed on a slide dries almost immediately, whereas when agar plates are poured they must first harden and then be dried for 60 to 90 min.

3) It uses only a fraction of the volume of culture medium required by the plate method.

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19 August 1954.

Original Adaptive Significance of the Tetrapod Limb

The origin of the tetrapod limb marked one of the major advances in the evolution of the vertebrates. The ancestral crossopterygian fishes had probably supplemented gill respiration with air breathing for a long time, but the reorganization of the paired fins into supporting legs and feet brought a major shift in genetic and functional emphasis, and opened the way for the extremely rich and complex evolution of the land vertebrates. The geologic record of tetrapod origin is still imperfectly known, and there has been much speculation concerning possible events in this transition. The tetrapod limb is usually interpreted as an adaptive modification that was directly useful for land locomotion in the relatively dry Upper Devonian, perhaps enabling the first amphibians to escape overland from receding swamps and pools to areas that might retain more water (*1*). Possible stages in evolution, from ancestral swimming fin through hypothetical intermediates to the walking leg, have been figured by several authors (*2–4*). This note considers an alternate selective advantage that this modification may have given to its first possessors: that, originally, the tetrapod limb may have served chiefly as a more efficient digging adaptation that facilitated estivation in the dry season.

Recent amphibians seek moisture and avoid dryness. Typically, they disperse from increasingly adverse, but still damp, sites only if the surrounding areas are sufficiently moist to attract, rather than repel, invasion. If the adjacent region is dry, they huddle into the damp debris and mud that remain from the evaporating pond. In semiarid climates the predominant amphibians are burrowing forms that can go underground to avoid desiccation. Newly transformed young amphibians normally linger in the vicinity of the pond margins until there is sufficient rain to permit dispersal, and the young of burrowing species commonly "dig in" soon after metamorphosis.

The extant groups of amphibians are, of course, greatly different from the original stock. The earliest known amphibians in the Upper Devonian were considerably larger than most of the modern forms, and in the adult stage they probably bore scales and were more effectively protected against desiccation. But their delicate young stages would certainly be vulnerable to environmental hazards, and a breeding population could not be maintained in an area for a geologically significant length of time unless the successive year-classes in the colony had reasonably continuous access to sufficient moisture to meet their basic needs.

The behavior of many extant vertebrates indicates that both land surface locomotion and burrowing can be carried on successfully without the tetrapod leg and foot. Certain fishes can make temporary or even regular land excursions. For example, the mudskippers (*Periophthalmus* sp.) and the climbing perch (*Anabas* sp.) are well known for their ability to move about on damp land surfaces (*5*). Many kinds of fishes (certain eels, flatfishes, and so forth) habitually secrete themselves in the loose sandy or muddy bottom of their aquatic habitat. Some of the major groups of burrowing land vertebrates are legless (caecilians, snakes, and certain families of lizards); but these legless tetrapods are derived groups, and subterranean habits are their normal way of life rather than a seasonal or occasional adjustment in behavior.

Inferences concerning the possible behavior and ecology of ancient fishes on the basis of habits of highly differentiated modern forms that are only remotely related to them must be made with caution. In some cases, however, there is geologic evidence to support such inferences. For example, it is well known that the extant species of lungfishes of South America and Africa are able to withstand seasonal drouth by burrowing into the mud and estivating, and recently Romer and Olson (*6*) reported the remarkable discovery of Permian lungfishes found in upright cylindrical burrows under conditions that indicate that the individuals had been fossilized in estivating sites. It is apparent that seasonal escape underground from a drying swamp is a very ancient behavior pattern in certain evolutionary lines of dipnoans. The possibility that some of the early crossopterygians were also capable of effective burrowing can only be speculated, on present knowledge. But the skeletal structure of the paired fins of the few crossopterygians in which it is well known, for example, *Eusthenopteron* (*2*), compared with the general trends of foot specialization in tetrapods, suggests that the foot (the part of the limb that has always been the most difficult to account

for) can be understood most easily if it is interpreted as, originally, a digging specialization. In *Eusthenopteron* the proximal elements in both the pectoral and the pelvic fins resembled fairly closely the corresponding tetrapod elements, but the distal units were radial bones that had no very clear tetrapod resemblances, and the fin terminated in a thin flap. Westoll (*3*) suggested, as had a number of earlier authors, that the digits and their adjacent supporting bones are new structures rather than remodeled fin elements, and he proposed the terms *archepodium* for the proximal elements that were derived from the ancestral fin and *neopodium* for the new distal structures. He postulated (*7*) that the tetrapod limb originated only once, and that its establishment in the affected population was relatively rapid.

A dry era, such as the Upper Devonian, would be a particularly inauspicious time for the emergence of aquatic animals onto the land. The prospective new environment would then be at its worst for such animals, and it would be much more likely to select adaptations that would permit more effective direct use of available water supplies. The evolution of the fin into a strong footlike structure with good muscular control over its terminal segments would seem to confer greatest immediate functional and ecologic advantage as a more efficient digging mechanism that would enable the proamphibian to remain in contact with the retreating moisture by following it downward seasonally (perhaps digging into more resistant sediments), and thus remaining in the vicinity of established seasonal water holes rather than wandering off into a hostile environment. It is possible that the amphibians long remained a small and obscure group, gradually gaining in relative importance as they outlasted the contemporary swamp fishes that were less well equipped to survive in restricted habitats in a difficult climate. The real acceleration in amphibian evolution probably began later, when climatic changes began to provide better all-year moisture conditions and to open up a greater variety of near-shore ecologic niches. With pedal structure, air breathing, and associated modifications already established, the amphibians would be preadapted to extend their activities onto humid land areas.

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20 September 1954.

Potential Errors in Spectrophotometry with Optically Dense Solutions

The recent availability of photomultiplier detectors for ultraviolet spectrophotometers has introduced a possibility for obtaining false optical density measurements when solutions of high optical density are studied. In this, and other laboratories, it has become common practice to determine increments of optical density by compensating for the background density with similar solutions as reference samples. In particular, reactions have been followed below 290 mμ in the presence of protein and nucleotides, which absorb strongly in this region. It has been noticed that the addition of a given amount of absorbing material to solutions of high optical density yields a density increment less than that given by an identical addition to a solution of low density.

One theoretical explanation for this observation is the failure of Beer's law because of association of molecules. This explanation does not apply to the dilute solutions of various compounds tested. Another explanation is found in the limitations of the optical instruments used. As is well known by students of optics, every monochromator gives, in addition to the selected wavelengths, a certain amount of light of random wavelength, the so-called "stray light." The purpose of this communication is merely to indicate how stray light can be a source of significant error when the photomultiplier is used.

The failure of the spectrophotometer to detect densities above a high background was noticed in this laboratory during studies on the enzymatic formation of nicotinic acid. In these the absorption spectrum of pyridine compounds in the region 260–270 mμ could not be detected in incubation mixtures, although it was easily determined after deproteinization. The ability of the spectrophotometer to detect densities above high backgrounds was subsequently tested with the Beckman DU spectrophotometer using dilute solutions of adenosine at 260 mμ, quinolinic acid at 268 mμ, urocanic acid at 277 mμ, and tyrosine at 280 mμ. In each case solutions were made to give theoretical densities of 1, 2, 3, 4, and 5 by diluting proportional amounts of a stock solution to a given volume with buffer. Theoretically, each cuvette read against the previous one (the first one against buffer) should give a density of 1. The observed values in a typical experiment with adenosine were 1.0, 0.96, 0.88, 0.575, and 0.15. Similar values were obtained with each of the other compounds tested.

It is possible to obtain valid measurements of high optical densities if the light used is sufficiently monochromatic. It is obvious that when the response of the phototube to unselected light approaches or exceeds that to selected light penetrating the background, further changes in the selected light will have little influence on the phototube output. Therefore, the solution to the problem lies in reducing the ratio of stray to selected light. It should be emphasized that stray light is an intrinsic property of the monochromator,

not a function of leaks. Also, stray light is distributed throughout the light beam and is not affected materially by changing slit widths. Decreasing the light path through the sample reduces the proportion of stray light but also causes a corresponding decrease in the magnitude of density read for a given sample. The proportion of stray light can also be reduced by the use of purer monochromatic light, which can be obtained with special light sources, filters, or additional monochromators. For example, when light from a mercury arc (H100-A4) passed through one Beckman monochromator was used as a source for a second Beckman spectrophotometer, accurate measurements could be made on solutions with background optical densities exceeding 5. Similar values were obtained with the Cary spectrophotometer, which has a double monochromator.

It is not practical to attempt to define specific limits of usefulness for any instrument, since the optical density at which serious errors are obtained is a function not only of the light source, monochromator, and phototube but also of the wavelength selected and the absorption spectrum of the samples. Therefore, each instrument must be tested with substances of known extinction, the backgrounds desired, and the required wavelengths in order to determine the conditions that permit accurate measurements.

The limitations of optical instruments discussed here have been understood by spectroscopists for many years. The purpose of this communication is to emphasize a source of error that may be significant in biological studies. I am indebted to Drs. F. Brackett and R. Olson for many helpful discussions.

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22 November 1954.

Sex Differences in the Packed Cell Volume of Vertebrate Blood

The existence of sex differences in the packed cell volume (PCV) of human blood seems to be established (*1*). Sex differences in PCV among the lower, as well as the higher, vertebrates is reported here.

Blood was obtained from the exposed heart in frogs (*Rana pipiens*) stunned by a head blow (*2*), from the axillary vein in unanesthetized pigeons (*Columba livia*), and by cardiac puncture through a cervical approach in unanesthetized turtles (*Pseudemys* sp.), and through the intercostal spaces in etherized guinea pigs (*Cavia porcellus*). Only mature animals were used.

Table 1. Statistical analysis of sex differences in the packed cell volume of vertebrate blood.

Animal and sex		No. of animals	Mean PCV (ml/100 ml blood)	t-values
Frog	M	304	30.1* ± 7.7	8.0
	F	233	24.8 ± 7.4	
Turtle	M	101	27.9 ± 7.0	3.6
	F	101	24.3 ± 6.5	
Pigeon	M	112	58.5 ± 5.9	2.63
	F	100	56.4 ± 5.6	
Guinea pig	M	67	47.1 ± 4.5	9.5
	F	67	39.8 ± 4.4	

* Mean ± standard deviation.

The Wintrobe method was followed (*3*), with the blood centrifuged for ½ hr at 3000 rev/min. The anticoagulant in frogs was 3 percent sodium citrate, added just to the lowest mark of the hematocrit tube. For the other animals, 0.8 g of potassium oxalate and 1.2 g of ammonium oxalate were dissolved in 100 ml of distilled water, 0.5-ml samples were withdrawn and dried, and to each sample 1 ml of blood was added. It is assumed that hematocrit corrections for anticoagulant were unnecessary and irrelevant to the present study.

Table 1 shows a statistically significant sex difference in the PCV in representatives of each vertebrate class studied. The Student t-test showed all differences to be significant at the 1-percent level. Among mammals, sex differences in PCV are controversial in dogs, rabbits, and rats (*4*).

HAROLD M. KAPLAN
Department of Physiology, Southern Illinois University, Carbondale

References and Notes

1. E. C. Albritton, *Standard Values in Blood* (Saunders, Philadelphia, 1952), p. 38.
2. I wish to thank William H. Paris for assistance in obtaining data on frogs.
3. M. M. Wintrobe, *Clinical Hematology* (Lea and Febiger, Philadelphia, 1942), p. 180.
4. H. D. Bruner and G. E. Wakerlin, *Proc. Soc. Exptl. Biol. Med.* **36**, 667 (1937); D. G. Cameron and G. M. Watson, *Blood*, **4**, 816 (1949); M. M. Wintrobe, H. B. Shumacker, Jr., and W. J. Schmidt, *Am. J. Physiol.* **114**, 502 (1936).

9 August 1954.

A paradox is never terrifying to the scientist. Faraday wrote to Tyndall, "The more we can enlarge the number of anomalous facts and consequences, the better it will be for the subject, for they can only remain anomalies to us while we continue in error."—GILBERT N. LEWIS, *The Anatomy of Science.*

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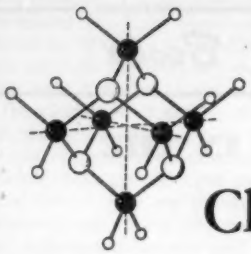

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24–27. American Soc. of Heating and Ventilating Engineers, Philadelphia, Pa. (A. V. Hutchinson, 62 Worth St., New York 13.)

26–2. Australian and New Zealand Assoc. for the Advancement of Science, Melbourne, Australia. (J. R. A. McMillan, 157 Gloucester St., Sydney.)

27. American Federation for Clinical Research, western section, Carmel, Calif. (A. B. French, College of Medicine, Univ. of Utah, Salt Lake City.)

27–28. Symposium on Hydrocarbon Chemistry, Houston, Texas. (L. B. Odell, Rice Hotel, P. O. Box 38, Houston.)

27–29. American Assoc. of Physics Teachers, New York, N.Y. (R. F. Paton, Dept. of Physics, Univ. of Illinois, Urbana.)

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28–29. Bur. of Biological Research, Rutgers Univ., New Brunswick, N.J. (W. H. Cole, College of Arts and Sciences, Rutgers Univ., New Brunswick.)

February

4–5. American Geophysical Union, Berkeley, Calif. (D. K. Todd, College of Engineering, Univ. of California, Berkeley 4.)

7–9. Conf. on Silicosis and Occupational Chest Diseases, Saranac Lake, N.Y. (N. R. Sturgis, Jr., Saranac Laboratory, Saranac Lake.)

7–11. American Soc. of Civil Engineers, San Diego, Calif. (W. N. Carey, 33 W. 39 St., New York 18.)

8–9. Midwest Welding Conf., Illinois Institute of Technology, Chicago. (Mel Garbar, Illinois Institute of Technology, 35 W. 33rd St., Chicago 16.)

11–25. Pan American Acad. of General Practice, Lima, Peru. (A. Martinez, 54 E. 72 St., New York 21.)

13–17. American Inst. of Mining and Metallurgical Engineers, annual, Chicago, Ill. (E. H. Robie, 29 W. 39 St., New York 18.)

14–16. Nutrition of Plants, Animals, Man. Michigan State College, Centennial Symposium, East Lansing. (Continuing Education Service, Kellogg Center, Michigan State College.)

14–19. Latin American Cong. of Physical Medicine, Lima, Peru. (C. L. de Victoria, 176 E. 71 St., New York 21.)

17–18. National Conf. on Transitor Circuits, Philadelphia, Pa. (W. J. Popowski, Minneapolis-Honeywell Regulator Co., 176 W. Loudon St., Philadelphia 20.)

17–19. American Acad. of Forensic Sciences, Los Angeles, Calif. (W. J. R. Camp, 1853 Polk St., Chicago 12, Ill.)

28–1. American Orthopsychiatric Assoc., 32nd annual, Chicago, Ill. (M. F. Langer, AOA, 1790 Broadway, New York 19.)

28–2. American Educational Research Assoc., St. Louis, Mo. (F. W. Hubbard, 1201 16 St., NW, Washington 6, D.C.)

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7–9. Chemical Inst. of Canada, Divisional Conf. of the Chemical Engineering Div., Ottawa, Ont. (W. M. Campbell, Box 323, Deep River, Ont.)

7–11. American Soc. of Photogrammetry, Washington, D.C. (C. E. Palmer, 1000 11 St., NW, Washington 1.)

7–11. National Assoc. of Corrosion Engineers, 11th annual, Chicago, Ill. (A. B. Campbell, 1061 M & M Bldg., Houston 2, Tex.)

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31–2. Soc. of Research in Child Development, Monticello, Ill. (C. B. Stendler, College of Education, Univ. of Illinois, Urbana.)

April

1–5. Japan Medical Cong., Kyoto. (M. Goto, Univ. Hospital, Kyoto Univ., Kyoto.)

2. Kappa Delta Pi, Cleveland, Ohio. (E. I. F. Williams, 238 E. Perry St., Tiffin, Ohio.)

3–6. American Astronomical Soc., Princeton, N.J. (C. M. Huffer, Washburn Observatory, Madison 6, Wis.)

3–7. American College Personnel Assoc., Chicago, Ill. (C. Evans, Univ. of Indiana, Bloomington.)

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4–6. American Assoc. of Physical Anthrolpologists, Philadelphia, Pa. (J. L. Angel, Jefferson Medical College, 307 S. 11 St., Philadelphia 7.)

5. Histochemical Soc. Symposium, Philadelphia, Pa. (A. B. Novikoff, Waldemar Medical Research Fdn., Port Washington, N.Y.)

6–8. American Assoc. of Anatomists, Philadelphia, Pa. (N. L. Hoerr, 2109 Adelbert Rd., Cleveland 6, Ohio.)

8–9. Pennsylvania Academy of Science, Philadelphia, Pa. (K. Dearolf, Public Museum and Art Gallery, Reading.)

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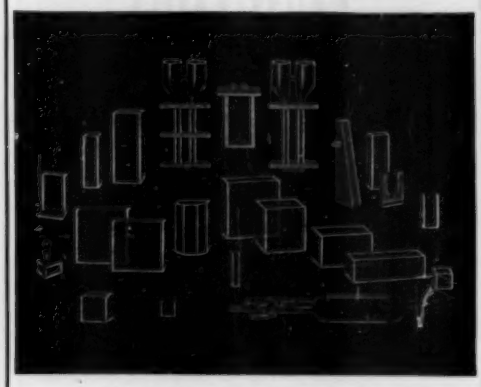

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12–15. International Union of Biological Sciences, 12th general assembly, Rome, Italy. (P. Weiss, 2101 Constitution Ave., Washington 25, D.C.)

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15–16. Iowa Acad. of Science, Davenport. (J. L. Laffoon, Iowa State College, Ames.)

16. Committee for the Scientific Study of Religion, spring, New York, N.Y. (W. H. Clark, Hartford Seminary Foundation, Hartford 5, Conn.)

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21–22. Eastern States Health Education Conf., New York Academy of Medicine, New York, N.Y. (NYAM, 2 E. 103 St., New York 29.)

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24–29. Inter-American Cong. of Radiology, Washington, D.C. (E. P. Pendergrass, 3400 Spruce St., Philadelphia 4, Pa.)

26–28. American Industrial Hygiene Assoc., Buffalo, N.Y. (H. F. Smyth, Jr., 4400 5 Ave., Pittsburgh 13, Pa.)

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April, *contd.*

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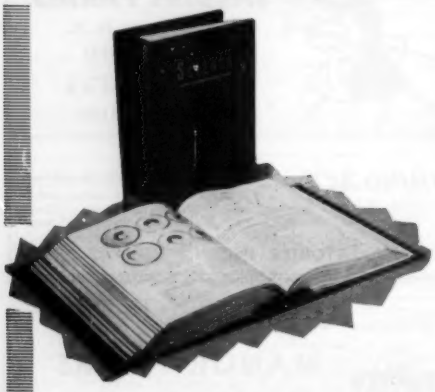

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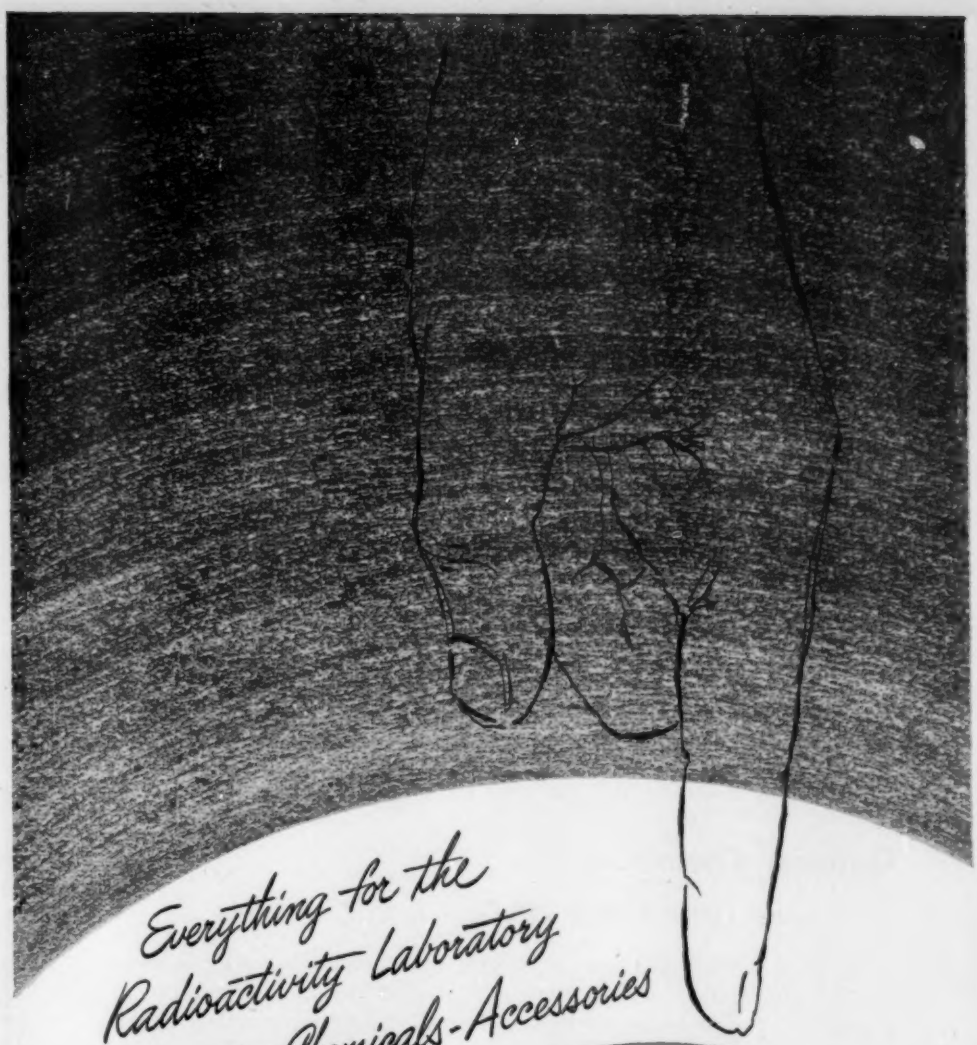

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